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 was diagnosed 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 community controls 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.

Genetic Influences in Irritable 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.

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 liquid load (a) or (b) is blocked by Dexloxiglumide, a CCK-1 receptor antagonist.

Results: (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 liquid load (a) or (b) is blocked by Dexloxiglumide, a CCK-1 receptor antagonist.

Conclusions: This study suggests that genetic factors do not contribute substantially to the aetiology of IBS.
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±158; Dex/C12: 1625±204; Sal/C12: 2112±210 (both 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 mucosal nerves, we injected a neuronal tracer, Texas Red, into the mucosal nerves, we injected a neuronal tracer, Texas Red, into the mcosa of 10 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 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 5 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 vanilloid receptor antagonist Capsazepine (5μM) and capsaicin (5μM) were studied.

Results: Preliminary dose ranging experiments suggested 2 populations of acid sensitive gastric cells based on threshold for activation (pH 6.7 or pH 5.8). Following this, pH 6.1 and pH 5 were chosen as low and high threshold stimuli respectively. 126 cells of gastric origin were analysed. Of these 20 responded to pH 5 but not pH 6.1. 16 of these cells were not capsacain sensitive and the response to acid was unaffected by capsazepine. In contrast only 3 cells with similar properties could be identified from 412 non-gastric cell controls (p=0.0001).

Conclusion: The gastric mucosa is innervated with high threshold non-capsacain sensitive nerves. These cells may be important in sensitizing acidification of the mucosa in response to injury, probably through activation of acid sensing ion channels.

005 5-HT, RECEPTOR AGONISM SUPPRESSES POST-PRANDIAL ANTROPYLORO-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 positioned by measurement of transmucosal PD) 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 (S) (6mg, 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: S27 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, 47) mmHg v 38 mmHg (21, 62) mmHg; p < 0.02), with neither antral (30 mmHg (15, 199) mmHg v 238 mmHg (231, 365) mmHg) or 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: 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 plateau-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 plateau-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 fluorimetric detection.

Results: Thirteen patients experienced abdominal pain and/or urgency with meal ingestion. These patients exhibited significantly higher postprandial levels of plateau-depleted 5-HT concentration than patients without any symptoms (postprandial area under the curve [AUC]; fasting AUC: with symptoms, 2.23 (adjusted geometric mean) v 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 with those “without” a postprandial exacerbation of their IBS symptomatology (peak: with symptoms, 18.5±3ng/ml v without symptoms, 8.7±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.


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 (66 [59–70]) p<0.001 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:** Psychophysicologists have demonstrated that learned autonomic responses can be produced in the gastrointestinal (GI) tract to 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 investigate 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 balloon attached was passed trans-oesally 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 phasic, 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 thin 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, inferior frontal cortex, periaqueductal 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.

**THE 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.

**Conclusion:** 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.

**HEALTH RELATED QUALITY OF LIFE IN PATIENTS SUFFERING FROM IRritable BOWEL SYNDROME**

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**Introduction:** Health related quality of life (HRQoL) is impaired in patients suffering from irritable bowel syndrome (IBS), but measurement of this remains poorly quantified. The treatment of severe IBS is often unsuccessful, although gut directed hypnotherapy has been shown to improve IBS symptoms but its effect upon HRQoL status has not been defined.

**Aim:** In this study we have defined the impact of gut directed hypnotherapy upon HRQoL status in IBS patients.

**Methods:** Seventy five patients (53 females; median age 37.1) with a diagnosis of IBS (consistent with Rome II diagnostic criteria) underwent gut directed hypnotherapy. The predominant symptoms were abdominal pain in 46 patients (61%), altered bowel habit in 24 (32.5%) and abdominal bloating in 5 (6.5%). Physical symptoms were prospectively recorded using seven day diary cards. Outcomes measures were Hospital Anxiety and Depression Scales (HAD-A & HAD-D) and a IBS disease specific quality of life tool (IBS-QoL). Measurements were taken at baseline (pre-treatment) and at three months (post-treatment). Pre and post treatment scores were coded and compared using Wilcoxon signed rank test.

**Results:** There were statistical improvements (p<0.001) in all domains of the IBS-QoL (emotional health, mental health, physical health, sleep, energy, diet, social role and physical role) after treatment. Improvements were most marked in female patients, particularly those with predominant abdominal pain. Significant improvements were seen for both males and females for anxiety and (HAD-A p<0.001; HAD-D p<0.05).

**Summary/Conclusion:** Gut directed hypnotherapy has a very positive impact upon psychological well being and HRQoL in IBS. This appears most effective in patients with a predominant symptom of abdominal pain and bloating. A randomised controlled study of hypnotherapy is recommended in IBS.
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 DXA 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 1.29 kg (median 1.25kg). 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 on thalidomide in the following two weeks was 1.75 kg (median 1.33 kg). The mean change in REE was 1.75 (95% CI –0.42, 3.91) on thalidomide. Despite greater awareness among consultants, 60 died and 104 did not use Manning criteria, 67 died and 100 did not use Rome criteria. Of 123 responding GPs, only 14 use Manning and 4 use Rome criteria.

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.

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 admissions). Diffuse Oesophageal Spasm (DOS), Nutcracker oesophagus and Achalasias, as defined by Spechler and Castell (Gut 2001;49:145–51), were the only motility disorders recognized as a cause 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. All patients had normal Thallium scan who were further investigated with OM and pH studies between November 1998 and May 2001 (2.5 years/60 admissions). 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.

Conclusions: Twenty patients had 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%) has been readmitted and one (1.6%) had further cardiac investigations (mean follow-up 1.5 years).

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.

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: Ten healthy subjects were studied using a dual channel pH electrode with 1 cm distance markings. The squamocolumnar junction (Z-line) was marked by attaching metal clips at endoscopic sites where 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 clips (Z-line) were shown. Kruskal-Wallis was measured in each subject under fasting conditions and 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 acid reflux region of the stomach (pH 5.4) (p < 0.01). This pocket of acid (defined as < pH 2) extended over 2 cm (range 1–4cm). The pH step-up distance moved after the meal [46.0cm fasting vs 44.4cm postprandial p < 0.05]. In contrast the distance to the Z line did not [46.3cm fasting vs 46.2cm postprandial]. The fasting pH step up corresponded to the Z-line and therefore the acid pocket extended from the cardia across the Z-line and 1.8cm into the distal oesophagus.

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, just above and just below the squamocolumnar junction.

Reference:

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

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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 to 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 performed to locate the LOS. Under ambulant conditions, pH was measured at 5cm above and at 2 and 10cm below the LOS.

Results: As expected, oesophageal acid exposure (% time pH < 4) was greater in patients than volunteers [pre-prandial 8.5 v 0.9 p<0.0002; prandial 4.0 v 1.1, p<0.04; 0 to 60 min postprandial 11.7 v 1.0, p<0.002; and while supine 13.7 v 2.3, p<0.001]. Gastric cardia acid exposure (pH at 2 cm below the LOS) showed marked variability but was again greater in patients than volunteers (table). Transient buffering of cardia pH was seen in patients during ingestion of meals but rapidly returned to pre-prandial values. Gastric body acid exposure [pH 10 cm below the LOS] was consistently high and was greater in patients than volunteers (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.

**017 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: To compare the accuracy of MBDB technique against random biopsy (RB) to detect intestinal metaplasia 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 >3cm 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 biopsies 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 methods were methylene blue stained).

Results: Fifty-seven patients were recruited, of whom 44 were male. The mean age was 60 years range (31–85). The mean length of Barrett’s was 3.4 cm, range (5–9). Using MBDB, 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: ID, LGD 21, HGD 2, Ca 2. Using RB technique 618 biopsies were obtained. SIM was present in 421 biopsies; mean 7.39 biopsies (68.12%). Dysplasia and carcinoma were diagnosed in 23 patients: ID 3, LGD 16, HGD 2, and Ca 2.

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.

**019 INTERPHASE FLUORESCENCE IN SITU HYBRIDISATION (FISH) ON BARRETT’S OSSOPHAGUS 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: Gastroscopy and biopsies were taken 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 BARRETTS’ ESOPHAGUS: AN IN VITRO MODEL**

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1 National Medical Laser Centre, Department of Surgery, Royal Free and University College School of Medicine, London; 2 Cancer Cell Unit, Hutchison/MRC Research Centre, Cambridge CB2 2ZX, UK

Background: Photodynamic therapy (PDT) is an emerging endoscopic 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: To investigate (a) differences in early repair (restitution) of an oesophageal cell monolayer following mechanical or PDT injury; (b) whether restitution can be altered by adding growth factors and cytokines.

Methods: Cell lines; Squamous (OE21), Barrett’s (OE33) and co-cultures were injured mechanically or with PDT (5–aminolevulinic 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-ß1), 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 (OE-21) underwent greater restitution than columnar cells (OE-33). In both mechanical wound and PDT assays of co-cultures, TGF-ß1 increased cell repair by restitution compared with controls (p<0.05). This effect was not seen in individually cultured cells. 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 SURVIVAL IS WORTHWHILE AND DETECTS CURABLE CANCERS**


University Hospitals Coventry and Warwickshire NHS Trust, UK

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 one year of surveillance and no patient had dysplasia 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 surgery. All had carcinoma in the resection specimen. Lymph nodes showed evidence of metastases in 10 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 (4% of group; 8% of those operated) and 7 patients in the surveillance cancer group (54% of group; 50% of those operated) 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 first cancer was detected per 48 patient years of surveillance (33/7).

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 ESOPHAGUS: EXPERIENCE FROM A DISTRICT GENERAL HOSPITAL**


Royal Bournemouth Hospital, UK

Background: The incidence of adenocarcinoma of the oesophagus is rising. Barrett’s oesophagus is regarded as a high risk premalignant condition for this cancer. The effectiveness of endoscopic cancer surveillance programmes is unknown.

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 an endoscopic 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 ESOPHAGUS**

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National Medical Laser Centre, Department of Surgery, Royal Free & University College School of Medicine, London, UK

Background: Photodynamic therapy (PDT) is a minimally-invasive alternative to oesophagectomy for high grade dysplasia (HGD) or intramucosal adenocarcinoma (T1a, AdCa) arising in Barrett’s columnar lined oesophagus. Initial reports using 5-aminolevulinic acid
(ALA) suggest that H. pylori 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 500–1000/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 “buried” 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 17 cm, non-responders 35 cm, 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 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.

A method has been developed whereby sutures can be placed via an endoscope just below the oesophago-gastric 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 cm. Pre-procedure assessment included symptom scoring, oesophageal endoscopy, manometry and 24 hour oesophageal pH, and completed QOL and adverse events were assessed at 1, 3, 6 and 12 months. Repeat endoscopy, manometry and 24 hour pH were performed at 3 months. Mean age was 37 (22 – 58 yrs.). All received conscious sedation (Midazolam and Pethidine). The median duration of the procedure was 50 minutes. The mean heartburn symptom score (heartburn frequency x severity) was 50 minutes. The mean heartburn symptom score (heartburn frequency x severity) was 50 minutes. The mean heartburn symptom score (heartburn frequency x severity) was 50 minutes. The mean heartburn symptom score (heartburn frequency x severity) was 50 minutes.

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.

Gastroduodenal free papers

026–032
A COMPARISON OF SYSTEMATIC REVIEWS OF HELICOBACTER PYLORI ERADICATION FOR NON-ULCER DYSEPSIS
J. Deeks, B. Delaney, D. Forman, P. Moayyedi. ICRF/NHS Centre for Statistics in Medicine, Oxford, UGPD Cochrane Group; University of Leeds, Primary Care Sciences Building University of Birmingham, UK.

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

Abstract 026

<table>
<thead>
<tr>
<th>Trials</th>
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<th>OR of cure</th>
</tr>
</thead>
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<tr>
<td>All abstracts</td>
<td>10</td>
<td>0.90 (0.86, 0.94)</td>
</tr>
<tr>
<td>All H pylori regimens</td>
<td>11</td>
<td>0.90 (0.86, 0.94)</td>
</tr>
<tr>
<td>Remove all 2000 trials</td>
<td>5</td>
<td>0.92 (0.86, 0.99)</td>
</tr>
<tr>
<td>Code adverse events</td>
<td>9</td>
<td>0.90 (0.86, 0.95)</td>
</tr>
<tr>
<td>Only published data used</td>
<td>9</td>
<td>0.90 (0.85, 0.95)</td>
</tr>
</tbody>
</table>

www.gutjnl.com
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, reducing the number of trials in the review and widening 95% confidence intervals. Use of the odds ratio increased heterogeneity and a random effects model yielded a non-significant overall effect. Other differences in methodology did not make a difference in this instance.

**Conclusions:** The results of this review in a fast developing field depend on inclusion of all relevant articles. The ability to continually update Cochrane reviews ensures that they are the more appropriate format for publishing reviews in research areas that are fast evolving.

**O27 EFFECTS OF HELICOBACTER PYLORI EXTRACTS ON ENDOTHELIAL CELL PROLIFERATION AND MIGRATION IN VITRO**

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**Background/Aims:** Helicobacter pylori (H. pylori) infection is associated with delayed healing of peptic ulcers which in turn is dependent upon angiogenesis or new blood vessel formation. Proliferation and migration of endothelial cells (ECs) are crucial stages of angiogenesis. 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 viability and Hoechst/Propidium Iodide staining identified apoptotic, necrotic and viable ECs. Migration in response to vascular endothelial growth factor (VEGF) was assessed 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 3 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 was observed. VEGF significantly increased control migration (P<0.01) which was not inhibited by any of the bacterial extracts. H. pylori extracts inhibit EC proliferation in vitro by a cytotstatic mechanism but do not inhibit EC migration. This anti-proliferative effect is also demonstrated by C. jejuni. Inhibition of EC proliferation may decrease angiogenesis, despite no effect on migration, at the ulcer site which may in turn explain the delay in ulcer healing associated with H. pylori infection.

**O28 STUDIES OF THE EFFECT OF H. PYLORI CAGA +VE VERSUS CAGA −VE ON ACID SECRETION IN HEALTHY VOLUNTEERS**


**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 i.e. gastrin concentration achieving 50% maximal acid output (MAO).

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

**Discussion:** The higher gastrin and lower sensitivity to gastrin in Cag+ves 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.

**O29 LAPAROSCOPY SIGNIFICANTLY IMPROVES 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.

**Abstract 029**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Computed tomography</th>
<th>Laparoscopy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>T</td>
<td>M</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>67</td>
<td>36</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>67</td>
<td>92</td>
</tr>
<tr>
<td>Kw</td>
<td>0.35*</td>
<td>0.30**</td>
</tr>
<tr>
<td>Kw 95% C.I.</td>
<td>0.18–0.53</td>
<td>0.11–0.49</td>
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</table>

*p<0.0001; **p<0.001.

**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% (Chi^2 12.65, P<0.0001) that would have resulted without laparoscopy.
030 THE EFFECT OF REDUCED QUALITY OF LIFE ON THE SUBSEQUENT DEVELOPMENT OF DYSPEPSIA AND IRRITABLE 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 13C-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), Duke’s Quality of Life Index (QoLI), Dyspepsia Quality of Life Index (DQWLI), Dyspepsia Impact Scale (DIS), Mano- naire and IBS by the presence of 3 or more Manning’s criteria. Assessments were made at baseline and at two years. Reduced QoL was defined as a PGWBI of <106 (the mean score at baseline).

Results: 769 participants were enrolled with baseline PGWBI > 106. Subjects that had dyspepsia or IBS at baseline were excluded. 71/576 (12%) of subjects with a PGWBI > 106 that did not have dyspepsia at baseline had dyspepsia at two years compared with 76/388 (20%) of subjects with PGWBI < 106 (relative risk [RR] = 0.62, 95% confidence interval [CI] = 0.47 to 0.85; p=0.003). 30/772 (4%) of subjects with a PGWBI > 106 that did not have IBS at baseline had IBS at two years compared with 67/622 (11%) of subjects with PGWBI < 106 (RR = 0.36, 95% CI = 0.24 to 0.55; p<0.0001). The associations between reduced PGWBI and subsequent development of dyspepsia and IBS remained in logistic regression models controlling for age, gender, H pylori eradication, NSAID use, social class, smoking coffee and alcohol intake.

Conclusion: Reduced QoL is an important risk factor for the subsequent development of dyspepsia and IBS. Drugs that improve these disorders may not improve QoL as much as cross-sectional surveys suggest.

031 PROTON PUMP INHIBITOR THERAPY REDUCES BIOAVAILABILITY OF DIETARY VITAMIN C

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Background and Aims: Vitamin C is denatured 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 high performance liquid chromatography (HPLC) 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 (44, 10–130) versus −ve (141, 23–282) (p<0.001) and in the former below the recommended minimum value of 60mg/day. The 4 week course of omeprazole lowered the mean plasma vitamin C concentration by 15% (p=0.005) 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 (92.3).

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.

032 GASTROINTESTINAL HAEMORRHAGE 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 low 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.

Endoscopy free papers

033 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 “New Deal” 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 and subspecialties.

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?

N. Sharma, K. Kane, R. Boulton. Department of Gastroenterology, University Hospital Birmingham NHS Trust, Birmingham

Background: Open access endoscopy is widely practiced in the UK and recent government emphasis on rapid access and assessment of suspected cancer has increased demand.

Aim: 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 with cancer had their notes reviewed for referral symptoms.

Results: See table. All patients with cancer under the age of 55 years had at least one alarm symptom of weight loss or dysphagia. OAE there were significant falls in both the average number of consultations (6.5 vs 5.7, p<0.05) and those for upper GI symptoms (2.2 vs 0.7, p<0.01). There were no changes for other GI symptoms (0.31 vs 0.30, p>0.05) and non GI symptoms (4.1 vs 4.7, p>0.05). The average drug cost per patient (£83.3 vs £82.9), the cost of drugs for dyspepsia (£64.5 vs £62.50) and for psychiatric drugs (£16.6 vs £16.0) did not alter significantly (p>0.05).

The number of investigations (38 vs 69, p<0.05), hospital referrals (132 vs 206, p<0.01) and admissions (21 vs 58, p<0.01) rose in the post endoscopy year.

Conclusion: The overall number of consultations and those for upper GI symptoms fell significantly in the year following endoscopy compared with the previous year, whilst those for other GI symptoms and non GI symptoms did not change. Overall prescribing costs did not alter whilst the number of investigations, hospital referrals and admissions rose significantly. A normal OAE confers little benefit to the patient and the GP.

Table 034

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Endoscopies</th>
<th>No. of cancers per group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 and over</td>
<td>2079</td>
<td>40 (1.92)</td>
</tr>
<tr>
<td>Under 55</td>
<td>1174</td>
<td>6 (0.51)</td>
</tr>
<tr>
<td>Total</td>
<td>3253</td>
<td>46 (1.41)</td>
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</table>

Conclusion: 36% of endoscopies were performed in under 55s. Upper GI malignancy was rare in this group. All patients in the younger group with cancer had symptoms that would have been appropriate referrals under urgent investigation of cancer guidelines. Recent meta-analyses suggest a ‘test and treat’ policy in young patients could be reduced if GPs which patients might be unsuitable for OAE.

DOES A NORMAL OPEN ACCESS UPPER GI ENDOSCOPY (OAE) RESULT IN BENEFIT TO THE PATIENT AND THE GP?

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

Introduction and aim: Stobhill Hospital offers GPs an unrestricted OAE Service. GPs receive a standard endoscopy report and no management advice is given. The aims of the study were to ascertain if a normal endoscopy changed the number of GP consultations, investigations, hospital outpatient referrals, admissions and drug prescribing costs in the year following the procedure compared with the previous year.

Study design: GP case records of every patient with a normal OAE over a 12 month period were scrutinised. Data collected included patient characteristics and past medical history. In the year preceding and following OAE, consultation rates, prescribing costs, the number of investigations, hospital referrals and admissions were obtained. Total drug costs were calculated for each patient.

Results: 247 patients were identified (150 females and 97 males). Age range 18-84 (mean 48.3 yrs). 13% had a past history of previous GI disease and 20% had a history of psychiatric illness. Following open access colonoscopy referrals.

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

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Introduction: Direct Booking, a part of the Government’s NHS plan, empowers patients to choose the timing of their forthcoming hospital appointment. This is intended to promote patient ownership of care. It is anticipated, as a consequence of this, that there will follow a reduction in hospital cancellations/rearrangements and an increase in attendances.

Aims: To re-design 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.
Open Access Colonoscopy: In the preceding 6 months, 619 were seen. The DNA rate was 5% and the cancellation & rearrangement rate was 32%. In the first 2 months of the new system, 189 patients were seen. The DNA rate and patient cancellation & rearrangement rate had fallen to 2% (p < 0.05) and 11% (p < 0.05) respectively. This new approach to the organisation of hospital appointments demonstrates that allowing patients to choose a convenient date, does result in a significant reduction in DNA and cancellation & rearrangement rates. This not only reduces time wasted in clinics and endoscopy sessions but also by administrative staff, secretaries, GPs and patients. The system is now being implemented across all of our GI subservices and will most likely act as a template for other departments.

AUDIT OF FAST TRACK 2-WEEK GI CANCER WAIT

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Aims: To audit the first 6 months of the 2-week cancer wait for Upper and Lower GI malignancy over 3-hospital site and 17 Consultant teams.

Methods: Prospective audit of a centralised fast tracked GI 2-week cancer referral system, GPs are offered either outpatient appointment or outpatient endoscopy. Main outcomes were to measure the number of patient’s referred and subsequent number of cancers diagnosed. The data was also analysed to assess (1) time from referral to assessment, (2) age and symptoms of those with cancers, (3) differential intake by GP practices.

Results: 87 GP surgeries were offered the service. A total of 263 patients were referred in the 6-month period. 112 upper from 38 GP practices (mean 2.8 patients per practice), 151 lower from 42 GP practices (mean 3.2 patients per practice). 25 cancers were detected, 7 upper (6.3%), 18 lower (11.3%). 50% of upper + 59% of lower GI referral were male. Age range was 25–89 years with 55% being 60–79yrs. Time from referral to initial assessment: upper < 1 week 56 patients (50%), < 2 weeks 54 patients (48.2%), >2 weeks 2 (1.8%) pt. Preference: lower < 1 week 57 patients (37.7%), > 2 weeks 91 patients (60.3%), > 2 weeks 3 patients (2%) pt preference. Age at diagnosis of carcinoma upper 1-50-59, 3-70-79, 3-80>, lower 4-60-69, 6-70-79, 6-80>. Symptomatic presentation of carcinoma, upper: GI: dyspepsia 2, dyspepsia + weight loss 2, dyspepsia + vomiting 4, dyspepsia + anaemia 2, dyspepsia lower: LG: abdominal mass 7, rectal mass 1, rectal bleeding + change in bowel habit +6 weeks 6, rectal bleeding – anal symptoms >60yrs 8, Iron deficiency anaemia 3. Outpatient appointment requests accounted for 34.8% of upper and 71.6% of lower GI referrals. Conclusion The proportion of diagnosed carcinomas is in excess of with the expected targets. The 2-week referral system has been successfully implemented despite logistic difficulties, but use of the system by GPs is patchy.

DOES PRE TREATMENT WITH A PROTON PUMP INHIBITOR (PPI) DELAY OESOPHAGO- GASTRIC CANCER DIAGNOSIS?

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Background: Previous presentations to the society have highlighted concerns over the use of PPIs and their potential to delay the diagnosis of oesophago-gastric cancer.

Aim: To determine whether PPI treatment prior to endoscopy results in delayed diagnosis of oesophago-gastric cancer in a district general hospital setting.

Method: A retrospective case notes audit of patients with oesophago-gastric cancer diagnosed within Morecambe Bay NHS Trust within the last year. All patient records identified with appropriate documentation were studied.

Results: A total of 62 case note records were identified. 21 patients (33.9%) were taking a PPI and 41 patients (66.1%) had not received a PPI prior to their first endoscopy. No significant difference was noted in the rate of missed cancers in either group. In those patients receiving PPI treatment one case of cancer was missed at first endoscopy (4.8%) compared to patients in the untreated group (4.9%). Interestingly, whilst the majority of endoscopies were performed by either consultant physicians or surgeons, all cases of missed cancer had their first endoscopy performed by a junior hospital doctor.

Conclusions: Preceding treatment with a PPI does not seem to delay the diagnosis of oesophago-gastric cancer. In contrast, cancers are more likely to be missed by relatively inexperienced endoscopists.

A 10 YEAR RETROSPECTIVE STUDY OF UPPER GI ADENOCARCINOMA. HOW CAN WE IMPROVE EARLY DIAGNOSIS?

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Background: The detection of Early Gastric Cancer (EGC) 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 or classified as carcinoids. The mean time from first investigation to diagnosis was 70 days (range 28–94). The symptoms at time of diagnosis included of anaemia/weight loss/dysphagia in 78.4%, epigastric pain (without alarm symptoms) in 10.1%, dyspepsia/ reflux/ heartburn in 6% and haematemesis/malaena in 5.3%. Of 665 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 consultation 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 had a previous gastroscopy within 3 years of diagnosis, whereas of the 328 prescribed AST prior to diagnosis this figure was 42.4% (p=0.01). 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 the time diagnosis decisions regarding treatment or investigation should not be based solely upon symptoms but on an overall assessment of risk.

EMPIRICAL ACID-SUPPRESSING THERAPY (AST) IS ASSOCIATED WITH DELAYED DIAGNOSIS OF OESOPHAGO-GASTRIC CANCER

S.J. Panter1,2, H. O’Flanagan3, M.G. Bramble1,2, A.P.S. Hungin1,2. 1James Cook University Hospital, Middlesbrough; ‘NoReN, Eaglescliffe Health Centre, Stockton on Tees

Aims: This retrospective study aimed to identify whether there are differences in the patterns of presentation of oesophago-gastric adenocarcinoma and so identify any potential to improve detection.

Methods: All upper GI adenocarcinomas diagnosed in South Tees Health District (population = 350,000) were identified from the hospital pathology and NYCRIS databases (April 1991 to April 2001). The GP records were reviewed and the data collected correlated with the pathology and hospital records.

Results: 747 patients were identified. 92% had primary adenocarcinomas (29% oesophageal, 71% gastric). 6% were excluded or classified as carcinoids. 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 had a previous gastroscopy within 3 years of diagnosis, whereas of the 328 prescribed AST prior to diagnosis this figure was 42.4% (p=0.01). 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.

Reference:

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 the time 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 gastrosopy 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 clinic 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.

**Abstract 043**  
PREDICTIVE VALUE OF ALARM SYMPTOMS IN DYSPESA 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 haemorrhage were excluded. Patient demographics, OGD indications, all symptoms including alarm symptoms, i.e. 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) 2.5), oesophageal ulcer (OR 9.1), oesophageal cancer (OR 24.7). Haematemesis was significantly associated with oesophagitis (OR 5.6). Melaena was significantly associated with gastric ulcer (OR 12.5), duodenal ulcer (OR 5.8). Anaemia was significantly associated with Barrett’s (OR 5.2) and oesophageal ulcer (OR 9.1). Abdominal pain was significantly associated with duodenal ulcer (OR 4.8). Chest pain was significantly associated with oesophagitis (OR 4.5). Atypical dyspepsia was significantly associated with oesophagitis (OR 2.9). Vomiting, weight loss were not associated with significant pathology.

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.

**Abstract 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 compared CLO™ +ve & CLO™ −ve patients, GP visits, Other GI investigations, Endoscopies, costs associated with CLO™ testing.

Methods: Consecutive outpatients 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™.

Costs per patient over year post randomisation

<table>
<thead>
<tr>
<th>Costs per patient over year post randomisation</th>
<th>Breath test only</th>
<th>Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopies</td>
<td>£16.83</td>
<td>£252.55</td>
</tr>
<tr>
<td>Breath tests</td>
<td>£20.96</td>
<td>£21.25</td>
</tr>
<tr>
<td>Other GI investigations</td>
<td>£0.98</td>
<td>£0.80</td>
</tr>
<tr>
<td>GP visits</td>
<td>£19.66</td>
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<td>Hospital visits</td>
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</tr>
<tr>
<td>PPI therapy</td>
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<td>£49.36</td>
</tr>
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<td>£16.04</td>
</tr>
<tr>
<td>Antacids/Alginates</td>
<td>£5.17</td>
<td>£6.11</td>
</tr>
<tr>
<td>Total</td>
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<td>£400.43</td>
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</tbody>
</table>

Conclusion: Non-invasive H. pylori testing is considerably more cost effective than endoscopy for the management of uncomplicated dyspepsia.

**Abstract 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.
Aims: To review our experience with Fibrin Glue (FG) injection 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 olate 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.
oncofetal carbohydrate antigens, TF (galactose [1,3-N-acetylgalactosamine] and sialyl-Tn [Tn, sialyl 2,6-N-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 glyco- protein epitopes amongst IBD twins.

Methods: Formalin-fixed rectal biopsies from 22 monozygotic twin pairs with IBD were studied (6 pairs discordant for UC or CD; 16 healthy twins). Affected twins were in clinical and endoscopic remission. Expression of Tn and TF was assessed by indirect immuno- histochemistry 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 Tn; 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 Tn positivity (Table).

Of the 5 unaffected twins who were Tn positive, 4 had twins with UC and 1 with CD. One of the Tn-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 mucosa-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 IL-10-/- mice with colitis.

Aims: The aetiology 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 trinitrobenzene sulfonyl 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 1 x 10⁷ 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 treated mice had significantly lower TNF-α 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.

**051** RELEVANCE OF THIOPURINE METHYLTRANSFERASE ACTIVITY IN INFLAMMATORY BOWEL DISEASE PATIENTS MAINTAINED ON LOW DOSE AZATHIOPRINE

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Background: It is well recognized that patients with low TPMT activity are more susceptible to developing bone marrow suppression side effects. In the UK, it is not uncommon to prescribe AZA at doses lower than 2 mg/kg body weight, but the relationship of the various dosing regimens on effectiveness of maintenance with reference to TPMT activity has not been investigated. We aimed to find the impact of TPMT activity on the clinical course of IB patients treated with low dose azathioprine (AZA, <2mg/kg).

Methods: We measured TPMT activity from blood samples from 113 IBD patients who were taking AZA, discontinued AZA because of side effects or had never taken AZA. TPMT activity was measured in 17 healthy controls. Relapse rates and time to first relapse were compared in IBD patients and stratified according to their TPMT activity.

Results: Patients who became neutropenic had a significantly lower mean TPMT activity, compared to the mean TPMT activity of patients who developed other side effects [ANOVA, p<0.05]. Patients who became neutropenic within the first 4 months maintained this degree of neutropenia throughout AZA therapy. Survival curves were constructed (time to first relapse) for low-dose AZA treated patients for TPMT activity of <20 nmol/hour/ml and >20 nmol/hour/ml. There were a lower number of relapses in IBD patients with lower TPMT lev-

Conclusion: Mean TPMT activity was significantly lower in patients on a low dose of AZA in remission compared with those that relapsed. TPMT activity was significantly lower in patients who discontinued AZA due to neutropenia than those who discontinued due to other side-effects. Though speculative, it is possible that the higher dose of AZA is only necessary in patients with higher TPMT activity. Our study results also provide an explanation for the commonly observed phenomenon of prolonged remissions on a low dose of AZA in a proportion of UK IBD patients.

**052** BEHÇET’S DISEASE AND TNF: A MISSING GENETIC LINK?

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Background: BD is a chronic multisystem inflammatory disorder associated with gastrointestinal tract inflammation in up to 50% of patients. Experimental and clinical evidence, most notably the efficacy of the anti-TNF agents infliximab, thalidomide and pentoxifylline, implicates TNF in disease pathogenesis. Association with HLA-B*51 has been reported worldwide but the relative risk varies widely suggesting this may be due to linkage disequilibrium (LD) with polymorphisms in nearby genes including TNFA.

Aims: To determine whether functional TNFA promoter polymorphisms are associated with susceptibility to BD.

Methods: LD mapping of 140 polymorphisms across 12 genes was carried out using PCR-SSP. Disease associations were evaluated at each biallelic SNP and by haplotype. 149 Caucasian BD patients and 350 healthy control subjects were studied.

Results: TNF-1031C was associated with disease (p<0.00003; RR 2.4; This allele was found on three TNF promoter haplotypes (T3, T6, T7) associated with disease (T3: P=0.03, RR 1.5, CI 1.1-2.3; T6: P=0.04, RR 3.5, CI 1.1-12.7; T7: P=0.001, RR 2.5, CI 1.4-4.3). Extended HLA haplotypes based on T3 and T7 were constructed. Peak RR on these was found of B*51 (RR 4.6 CI 2.6-7.7) and B*57 (RR 3.1 CI 1.7-5.6) respectively. The association with B*51 was found to be
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 of predisposing NOD2 variants 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 into a large number of subregions (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 (non-synonymous SNPs - Arg702Trp and Gly908Arg) 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). (Perianal: MICA*010, P=0.01, RR=2.1; Colon: BAT1A, 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 genotypes. (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 common in UK Crohn’s disease, whereas the Gly908Arg mutation is rare. The Leu1007fsinsC mutation is also common in UK Crohn’s disease, whereas the Gly908Arg 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.

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 ASPTRAN transmission disequilibrium test (TDT) and case-control association analyses were performed. (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 Arg702Trp (TDT Transmitted/Untransmitted 65/37, P=0.01, allele frequency in unrelated CD cases 10.6% vs. HC 2.8%) and Leu1007fsinsC (47/79, P<0.0001, 7.1% vs. 2.2%) mutations. No association was seen with Gly908Arg (11/12, P=0.1, 1.9% vs. 0.7%). Estimates 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.

[055] IMPORTANTANCE 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 typed 580 accurately characterised Caucasian CD patients (236 UC, 344 CD). Population frequency of NOD2 variants and association analyses were performed.

Results: Population frequency of NOD2 variants was Arg702Trp 14%, Leu1007fsinsC 10%, all tested mutations 23%. Genotype relative risk of CD was 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 protein 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 typed 580 accurately characterised Caucasian BD patients (263 CD, 317 UC) and 341 healthy controls. Three synonymous HSP70-1 SNPs (A1-110C, G190C, C438T) and two non-synonymous HSP70-1 SNPs (T2437C, G2763A) were studied using PCR-SSP.

Results: Six HSP70 gene haplotypes were constructed from the five biallelic SNPs. H1 (AGTGC) conferred protection to CD overall

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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 a $\chi^2 = 3.67$, $p = ns$.

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/infec tious agents in the later onset of juvenile CD.

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

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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=64) 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 proctocolectomy, 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.
**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 BPSUSSGRU UK incidence survey of IBD in those aged less than 20 years (N=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. (R² = 0.29 for CD and 0.43 for UC). However a likelihood ratio test showed these models not to be significant. Better description of the data than a straight line (χ²(6df) = 4.11; P=0.6613 for CD, χ²(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 find any significant periodicity in month of birth of either CD or UC cases.

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**Treatment of severe corticosteroid unresponsive ulcerative colitis by selective granulocyte and monocyte apheresis**

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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 clearly 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 GMCAP, we used a column of 335 ml capacity filled with 220g cellulose diacetate beads of 2 mm in diameter as the column adsorptive carriers (Adacolum). The carriers selectively absorb granulocytes and monocytes. Thirty one patients with prednisolone unresponsive severe UC and 8 corticosteroid naive patients with severe UC received 10 GMCAP treatment sessions, one session/week for 10 consecutive weeks. Duration of one GMCAP session was 60 minutes, flow rate 30mL/minute. The efficacy of GMCAP was assessed by measuring UC clinical activity index, UC disease activity index and Matts’ 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 naïve 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 GMCAP 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 followings, 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 corticosteroid.

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**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 was performed of the records of 20 patients treated with MMF over a 30-month period.

**Results:** Twenty patients (M=6 F=10, 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**

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**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 angiodyplasia (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 more than 100 units of blood, a directed surgery caused (2) or markedly reduced (1) the bleeding. Patients always preferred capsule endoscopy to push-enteroscopy (p<0.001). There were no complications. Preparation with picolax 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, lambangeptic 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.

Background and Aims: Our aim was to determine the prevalence of undiagnosed adult coeliac disease in the general population of England and in volunteers. Undiagnosed coeliac disease in the general population may have an increased prevalence of osteoporosis and mild anaemia. In contrast, they have a favourable cardiovascular profile which may provide substantial protection from ischaemic heart disease and stroke.

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 may provide substantial protection from ischaemic heart disease and stroke.

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=0.005 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=0.011). 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.

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

**Methods:** 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 loaded onto 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 50 ppm ("Negative test"), 50–200 ppm or greater ("Positive") and more than 10% gluten ("Strong positive"). Gliadin content of the test and control samples was determined using a direct sandwich ELISA that utilised a monoclonal antibody to omega gliadin. See table.

### Summary
Gluten can be readily detected in alcoholic beverages using dry strip immunochemistry. Results from GHT and ELISA broadly correlate. Kits may be useful for coeliacs to guide choice of alcoholic beverage.

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**067** ASSOCIATION OF COMMON HFE GENE MUTATIONS WITH COELIAC DISEASE RESULTS IN PROTECTION AGAINST IRON DEFICIENCY ANAEMIA

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**Introduction:** Coeliac disease (CD) and haemochromatosis are common conditions in populations with Celtic origins, but are associated with different defined human leucocyte antigen (HLA) haplotypes.

**Aim:** To determine if a genetic relationship exists between the two diseases, and if HFE mutations protect against iron deficiency anaemia.

**Methods:** Polymerase chain reaction amplification using sequence specific primers capable of identifying the 2 HFE gene mutations (H63D and C282Y), and the HLA class I and II alleles was used to type 77 Caucasian patients with CD, and 187 matched controls. Haemoglobin and serum iron were measured at diagnosis.

**Results:** The two HFE gene mutations were identified in 36 patients with CD (46.7%), and in 61 (32.6%) of the controls (P=0.035). Amongst the control population, the C282Y mutation was strongly associated with the HLA A*03 and B*07 alleles and H63D with the HLA A*25 allele but these associations were not observed in the CD group. By contrast, the C282Y mutation in the CD patients was associated with the HLA A*01 and B*08 alleles. CD patients with a C282Y mutation had significantly higher mean haemoglobin and serum iron compared to the HFE wildtype (P=0.04 and 0.0015 respectively). No such relationship was found for the H63D mutation.

**Conclusions:** HFE gene mutations are common in patients with CD. Different linkage disequilibrium between HFE mutations and HLA alleles in the CD and control groups allows for selection of HFE abnormalities in the disease, and a disease-specific haplotype which carries C282Y and DBP*0102 is suggested. In the context of CD we propose that HFE mutations provide a survival advantage by ameliorating the iron deficiency seen in this condition.

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**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 response 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 100 mg 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 positioned in 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 nor 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 (P=4).

**Conclusion:** A peptide corresponding to residues 57–75 of α-gliadin, exacerbates coeliac disease in vivo.

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**070** BONE MINERAL DENSITY IN ANOREXIA NERVOSA: NO CHANGE OVER TIME

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**Introduction:** Patients with anorexia nervosa (AN) are at high risk of osteoporosis. Body composition is also abnormal. The mechanisms behind these changes are unclear although oestrogen status and nutritional factors are believed to play a part. There is little information about the natural history of osteoporosis in patients with ongoing disease.

**Methods:** To investigate the natural course of bone mineral density (BMD) and body composition in AN, measurements were made using dual energy x-ray absorptiometry. We studied 16 adolescents (15–19 yrs) and 31 adults (>20yrs) all females, none had primary amenorrhoea. Local age and sex-matched controls were used for comparison with the adult group. We monitored the change in BMD and body composition of 13 patients over a mean follow up period of 21 months.

**Results:** In keeping with earlier studies, our adult anorexic patients had significantly lower BMI (16.2 vs 22.2 kg/m²), BMD (PA Spine T score -1.92 vs 0.2, total body WHO T score -1.2 vs 0.4), lean body mass (34.8 vs 38.3 kg) and fat mass (6.5 vs 19.2 kg) than the controls (all p<0.0001). The adolescent group did not differ significantly in either BMD or body composition from the adult group. Disease profiles were compared between adolescent and adult patients. Despite a shorter duration of illness (3.1 vs. 8.4 yrs p=0.01) and of amenorrhoea (2.6 vs. 5.8 yrs p=0.06) the adolescents’ BMD did not differ significantly from the adults. This may be due to the earlier onset of disease in adolescents (14.2 vs. 17.6 yrs) i.e. before peak bone mass is achieved. Using WHO definitions 37% of our patients had osteoporosis and 44% had osteopenia. In the 13 follow up patients there was no significant change in weight over time, despite ongoing psychiatric support. The BMD of these patients did not alter significantly over the follow up period.

**Conclusions:** Patients with AN have a significant reduction in BMD. Despite psychiatric support they remain underweight but...
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 – 71yrs, 8 males, 18 females, were recruited via gastroenterologist 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 analysis 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 or 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 dietetic assessment is required in the majority of patients to identify those with sub-optimal intakes (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 (7–6777) [20F:13M]. 25 patients (75%) 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 (1) 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 [2F:5M]. Indications for ITx were recurrent thromboses (4), recurrent central venous catheter (CVC) sepsis (3), and PN-related liver 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/6J-ApcMin) to investigate the action of low fibre diets 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) 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) on polyp progression, cell proliferation and crypt fission.

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 and high vitamin content may be a risk factor.


Abstract 072

<table>
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<th>Group</th>
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<th>Infection/HPN day x100</th>
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<td>0.03</td>
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<tr>
<td>ITx patients</td>
<td>7</td>
<td>8379</td>
<td>0.43</td>
<td>0.10</td>
</tr>
</tbody>
</table>

There were no differences between the groups in intestinal anatomy.

IS THE CURRENT SERVICE FOR THE INSERTION OF ENDOCOSMIC 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 (above 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 an insertion 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.

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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 seems 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 lambda carrageenan (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 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 leukocyte count. 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 colonic 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 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 ± 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 are 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 2 of unrelated causes. No deaths were related to HPN. 19 patients (22.3%) developed a confirmed line complication -10 (11.8% with catheter-related infection), 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 ± 1.05 months (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 (47 years ± 37.5 months) than those who died (55.3 years ± 64.4 months) and those that continued on HPN (50. Byers et al. 1994), 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.

### 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 5 ml organ baths containing warmed and oxygenated Krebs and isometric tension recordings made. Preparations were exposed to a cumulative concentration of zaprinast (3x10^-7 M to 3x10^-5 M), firstly paired with time controls and then in the presence and absence of N-nitro-L-arginine methyl ester (L-NAME, 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^-5 M).

**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 100µM L-NAME, the response to higher concentrations of zaprinast was significantly reduced (p<0.05, Student’s t-test) but not abolished: 30µM zaprinast (L-NAME) 72.4%±4.9% (n=7). SNP caused a concentration-related relaxation of the sphincter (EC50 3x10^-7 M) that was enhanced in the presence of zaprinast (EC50 1x10^-5 M) (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 cancer. 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.
Thirty patients (46%) 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.

**ANALYSIS 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 targeted 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). A biopsy was collected in the left hemi-colon (CSBH), in the left latero-anterior colon (LS), the middle (MD), and the right colon (BS). The number of polyps recorded was 36 (range 1–40). 12 patients (75%) 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, polyp, sex and age). The incidence of change of bowel habit (CBH), loose stool (LS), mucus discharge (MD), blood mixed with stool (BS), weight loss, palpable abdominal mass and mass palpable per rectum were significantly increased in the cancer group. Further, in the cancer group, symptoms of CBH, LS, MD and BS were significantly 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 Bifidobacterium longum and Lactobacillus acidophilus (HLC; Culcheth Ltd, Port Talbot, UK) has been studied in patients undergoing eradication of Helicobacter pylori by antibiotics.

**Methods:** 50 patients positive for H. pylori serology were recruited into the trial (8 were excluded for non-compliance). Patients were randomised into three treatment groups: antibiotics days 1–7 (metronidazole 400mg tds, amoxicillin 500mg qds, lansoprazole 30mg bd), with placebo days 1–15 (n=9), or the same antibiotics days 1–7 with probiotics days 1–15 (n=7), or the antibiotics with placebo days 1–7 and with probiotics days 8–15 (n=6). Patients provided stool samples on days 1, 7, 12, 17 & 27. Stools 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 enterobacteria between days 8 and 17 (p=0.025); 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**

M.A. Silva, G. Ratnayake, K.I. Deen. University Surgical Unit, Teaching Hospital of North Colombo, Ragama, Sri Lanka

**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). 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 NEOTERMIAL 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 polyposis 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 in separate groups (cancer, polyp, sex and age). The incidence of CIBH, LS, MD and BS were significantly 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.
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; median age 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; 2; 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 – 10 mm Hg vs 62 mm Hg – P<0.005 – Wilcoxon Rank Sum Test).

**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 rectoapexy has been used to correct this abnormality in an attempt to improve OD. The aim of this study is to assess patient’s perspective of the functional outcome of rectoapexy.

**Methods:** Thirty-six patients (male 2; female 34, median age 54 years, range 20–71) who underwent rectoapexy 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 rectoapexy. Ten patients (37%) were satisfied with the outcome of surgery. Five patients (19%) would recommend a rectoapexy 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 rectoapexy for OD. The overall patient satisfaction following rectoapexy for OD is less than ideal. Hence careful patient selection and counselling prior to surgery is essential.

**085 MAGNETIC RESONANCE IMAGING IN THE ROUTINE FOLLOW-UP OF COLORECTAL CANCER PATIENTS**


**Background:** Traditional policies for follow-up of colorectal cancer patients after curative surgery often detect recurrent disease at a stage in which palliation is the only option. We proposed to determine if a protocol of routine screening Magnetic Resonance Imaging (MRI) improves the detection of resectable recurrent colorectal cancer.

**Methods:** A cohort of colorectal cancer patients, who underwent curative surgery between 1995 and 1999, were included in a follow-up programme employing routine MRI scans at 3–6-month intervals, in addition to established clinical, biochemical and endoscopic tests. For patients with rectal and left-sided colonic tumours both the liver and pelvis were imaged, whereas patients with right-sided colon cancers underwent liver surveillance only. Cases were analysed for the impact of MRI on the detection of resectable recurrent disease and survival rates.

**Results:** Of the 278 patients who underwent MRI liver surveillance, 34 (12%) developed liver metastases over a mean follow-up period of 20 months (inter-quartile range 12–26). MRI detected liver metastases with 88% sensitivity and 90% specificity. Hepatic metastases were diagnosed solely by MRI in 14 cases (48%). Only 5 patients (15%) were eligible for hepatic resection and are alive 32–45 months after surgery. All cases unsuitable for surgery died with a median survival time of 10.5 months after diagnosis (IQ range 5–17.5). Pelvic recurrence was observed in 29 (13%) of the 217 patients who underwent regular pelvis MRI examination over a median period of 21 months (inter-quartile range 12–27) follow-up. Recurrent pelvic disease was detected by MRI with 83% sensitivity and 84% specificity. In 8 patients (27%) with pelvic disease MRI was the sole positive test. Surgery with curative intent was possible in only 5 cases (21%). None of the patients with local recurrence was alive after a median period of 9 months (IQ range 6–22) follow-up.

**Conclusions:** Routine follow-up by MRI may contribute to the detection of resectable liver metastases but has little impact on the diagnosis of recurrent pelvic disease at a stage when curative therapy can be successfully undertaken.
**087 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 polypectomy 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 type: 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 cm (range 0.2–6.0 cm). Nine hyperplastic polyps were COX-2 negative and one 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 within epithelium having 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 chemopreventive agents for this disease.

**088 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 (NS) at Osaka City University Hospital, Japan (OCU). FAP, HNPCC and IBD 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:** (1) 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.

**089 THE INFLUENCE OF ANTIBIOTICS ON IRRITABLE BOWEL SYNDROME: A RANDOMISED CONTROLLED TRIAL**

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**Introduction:** 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 therefore investigated 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 practitioners. H. pylori infection was assessed 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:** 1,713/2,329 (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 63/729 (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 = 0.53; 95% CI = 0.3 to 1.0; p = 0.03) and loose stool (OR = 0.43; 95% CI = 0.2 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). The TUNEL method was used to identify apoptotic cells. Indeed, in those subjects without IBS at baseline, antibiotic prescription appears to be protective.

**090 IS THE PS5-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 problematic. 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 (15 Gy). Patients’ aged was between 27 and 77 years (median 57.1), 13 males. 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, BCL-xL, Bax, Ki67, & P21/WAF1. The proliferative index (PI) was the percentage of cells positive for BCL-xL. The TUNEL method was used to identify apoptotic cells, the apoptotic index (AI) being the percentage of positive tumour cells.

<table>
<thead>
<tr>
<th>Abstract 088</th>
<th>Polypoid</th>
<th>Flat</th>
<th>Depressed</th>
<th>Adv. Cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMH—UK (%)</td>
<td>203 (79.6)</td>
<td>43 (16.9)</td>
<td>3 (1.2)</td>
<td>6 (2.4)</td>
<td>255</td>
</tr>
<tr>
<td>OCU—Japan (%)</td>
<td>216 (83.0)</td>
<td>35 (13.5)</td>
<td>6 (2.3)</td>
<td>3 (1.6)</td>
<td>260</td>
</tr>
</tbody>
</table>

*p=0.7151 Fisher’s Exact test
Results: After radiotherapy, the average AI increased significantly increased (2.2 ± 0.7 vs. 5.4 ± 0.8; p < 0.001). In contrast, the proline-rich activity (PI) decreased slightly (48.3 ± 4.2 vs. 42.7; p < 0.05). Bax immuno-staining was in 326 (11.5%) of biopsies and in 1526 (57.7%) of surgical specimens. Regarding other proteins, there were no significant differences between paired specimens. In surgical specimens, tumours with low expression for p53 (p233) showed a high AI and a low PI, in contrast with those with p53-H. Combination of p53 and p21/WAF1 revealed a subgroup p33(+) / p21/WAF1(+) with the highest AI (10.3) and the lowest PI (30.4) of all subgroups. Considering Bcl-2/Bax balance, tumours with Bcl2 (+) / Bax (+) showed a high AI (9.7) and the lowest PI (28.5). In contrast, Bcl-2(-) in the p53 (+) was associated with the highest PI (59.0).

Conclusion: Apoptotic cell death and up-regulation of Bax protein were induced by radiation in vivo. These results confirm a previously suspected important local effect of the p53-apoptotic pathway after short course preoperative radiotherapy.

Immunology/Infection/Inflammation free papers 091–104

091 HELICOBACTER PYLORI UPREGULATES MMP-7 IN EPITHELIAL CELLS IN A CAG-DEPENDENT MANNER

J.R. Bebb1, D.P. Leiley1, R.J. Thomas1, H.M. Collins1, S.A. Watson1, J.C. Athern1. Division of Gastroenterology and Institute of Infections and Immunity, Academic Unit of Cancer Studies, University Hospital, Nottingham, UK

Background: MMP-7 (matrixin) 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 the cagPAI (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 used for RNA extraction and reverse transcription, and cDNA levels assessed for MMP-7 levels (and GAPDH) by Real Time PCR. HT29 supernatants were assessed for MMP-7 expression by western blot and casein zymography and for other metalloproteinase activity by gelatin zymography. Experiments were performed at least three times.

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-independent but CagE-dependent. 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 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 Cag-dependent signalling and we speculate that it may be important in the pathogenesis of H. pylori.

092 SERUM IgG4 ANTIBODIES TO COMMON FOOD ANTIGENS ARE ELEVATED IN IRRITABLE BOWEL SYNDROME (IBS)

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Introduction: Food hypersensitivity is a common perception amongst IBS patients. Data from the dietary elimination and food challenge studies support the role of diet in the pathogenesis of IBS, but there are no well-established tests to identify food hypersensitivity.

Aim: To compare the serum IgG4 antibody titres to common food antigens in IBS patients and healthy controls.

Methods: 52 IBS patients [33 diarrhoea-predominant (D-IBS); 13 constipation-predominant (C-IBS); 6 mixed symptoms] and 18 healthy controls were studied. All patients underwent thorough clinical examination, routine blood tests and either a colonoscopy or sigmoidoscopy + Ba enema. Serum samples were tested for IgG4 antibodies to 10 common food articles including milk, eggs, wheat, rice, potatoes, chicken, beef, pork, fish and peanuts. A quantitative assay, carried out in a central laboratory, measured antibody titres in the range of 1.5–30,000MgA/L. Mann Whitney-U test was used to assess difference in the antibody titres to individual food antigens between IBS patients and healthy controls.

Results: IBS patients had significantly higher IgG4 antibody titres to milk (p=0.037), peanuts (p=0.04), beef (p=0.013), pork (p=0.001) and chicken (p=0.009) compared to healthy controls. The D-IBS group had significantly higher titres against peas (p=0.014), beef (p=0.017), pork (p=0.002), chicken (p=0.017) and wheat (p=0.038) compared to controls. The difference in milk antibodies was not significant (p=0.058). In the CIBS group, IgG4 titres were significantly higher for pork (p=0.018) and chicken (p=0.038) compared to controls. DIBS patients had significantly greater IgG4 titres to wheat (p=0.023) compared to CIBS group. The antibody titres to potatoes, rice, and eggs were not significantly different between the two groups.

Conclusion: Serum IgG4 antibodies to common food antigens like beef, pork, chicken, peanuts, wheat and milk are elevated in IBS patients. In keeping with the observation in other atopic conditions, this finding suggests the possibility of a similar pathophysiological role for IgG4 antibodies in IBS patients. The observation that the difference in antibody titres was predominantly observed in the DIBS group further strengthens this theory.

093 IS THERE A ROLE FOR MMP19 IN GUT INFLAMMATION?

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Introduction: The matrix metalloproteinases (MMPs) comprise a family of 26 enzymes, which modulate 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=1), 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, ileum, duodenum and 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 mucosa, stromal tissue including mononuclear cells and pericryptal fibroblasts. Increased expression of MMP19 was identified in IBD and coeliac disease.

094 ATTENUATION OF THE HEPATIC INFLAMMATORY RESPONSE TO PORTAL ENDOTOXIN XEMIA IN OBSTRUCTIVE JAUNDICE USING A NOVEL ANTI-ENDOTOXIN PEPTIDE.

M.A. Taylor1, J.M. Black1, A. Wallace1, M. Hopen1, W.D.B. Clements1, N.V. McFerran1, T. Diamond1, M.C. Regan1. 1Department of Surgery and 2Centre for Peptide and Protein Engineering, The Queen’s University of Belfast, Northern Ireland

Background: In obstructive jaundice (OJ), hepatic proinflammatory cytokines such as TNFα and IL6 are released in response to portal

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Gut: first published as 10.1136/gut.50.suppl_2.a107 on 1 April 2002. Downloaded from http://gut.bmj.com/
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 Re995. A test peptide, P6, was developed which was shown to inhibit LPS-induced TNFα secretion by human monocyctic 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. A significant effect on neutrophil outgrowth. Enterotoxins and NGF have an additive effect: 1.0 µg/ml CT and 1.0 µg/ml LT induce neurite outgrowth with NGF by 55% and 15.4% respectively (p<0.05). This significant effect on neurite outgrowth. Enterotoxins and NGF have an additive effect: 1.0 µg/ml CT and 1.0 µg/ml LT induce neurite outgrowth with NGF by 55% and 15.4% respectively (p<0.05). This effect was not seen with StA, however StA did increase cell diameter in the presence of NGF (p<0.05).

**Conclusion:** These observations support the hypothesis that enterotoxins have a direct effect on neuronal cells. CT and LT induce neurite outgrowth in PC12 cells and enhance the neuronal differentiation effects of NGF. StA does not induce neurite outgrowth alone but does appear to change the morphology of PC12 cells in the presence of NGF.

**Abstract O94**

<table>
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<tr>
<th>T min</th>
<th>TNFα</th>
<th>IL6</th>
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<tbody>
<tr>
<td></td>
<td>LPS alone</td>
<td>LPS + P6</td>
</tr>
<tr>
<td>80</td>
<td>4390* (4179–4983.8)</td>
<td>3118 (406–3761)</td>
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<tr>
<td>100</td>
<td>5451* (4635–6233.2)</td>
<td>3951 (644.5–4334.5)</td>
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<tr>
<td>120</td>
<td>6186.5* (5406.3–7214.3)</td>
<td>4409 (74.4–5872.5)</td>
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</tbody>
</table>

All data are median (Interquartile range) * P<0.05 versus LPS+P6 [Mann-Whitney U Test].

**CHOLOERA TOXIN (CT), ESCHERICHIA COLI HEAT LABILE TOXIN (LT) AND HEAT STABLE TOXIN (STA) HAVE A DIRECT EFFECT ON THE NEURONAL-LIKE PC12 CELL LINE**

A.C. Casburn-Jones1, S.C. Barnett, U.F. Fitzgerald2, M.J.G. Farthing2. 1Dept Medicine, 2Dept Neuroscience, University of Glasgow, UK

Evidence exists that CT, LT and StA mediate intestinal secretion through an enteric neural reflex arc. Enterotoxins may activate a secretary response by binding directly to the enteric nervous system. To investigate the direct effect of these toxins on neurons we used PC12 cells, a neurogenic cell line derived from a rat phaeochromocytoma. PC12 cells have been used as a model system for neuronal differentiation and neurite outgrowth. After stimulation with nerve growth factor (NGF) PC12 cells change from a chromaffin-like to a neuronal-like phenotype.

**Method:** PC12 cells were grown on poly-L-lysine coated coverslips in 24-well plates in defined serum-free medium (termed SATC) for 24 h. CT, LT and StA, (0.01–2.0 µg/ml), were added to the culture media.

**Results:** NGF induces neurite outgrowth: 60.7% of PC12 cells in the presence of NGF have neurite(s) = 1 cell diameter compared to 1.84% of control, (p<0.005). CT and LT alone induce morphological alterations similar to NGF-differentiated PC12 cells: CT and LT induce neurite outgrowth and branched spikes of tips of neurites. 1.0 µg/ml CT and 1.0 µg/ml LT result in 16.4% and 25.8 % of cells bearing neurite(s) = 1 cell diameter, respectively, (p<0.005). StA alone has no significant effect on neurite outgrowth. Enterotoxins and NGF have an additive effect: 1.0 µg/ml CT and 1.0 µg/ml LT increase neurite outgrowth with NGF by 55% and 15.4% respectively (p<0.05). This effect was not seen with StA, however StA did increase cell diameter in the presence of NGF (p<0.05).

**Conclusion:** These observations support the hypothesis that enterotoxins have a direct effect on neuronal cells. CT and LT induce neurite outgrowth in PC12 cells and enhance the neuronal differentiation effects of NGF. StA does not induce neurite outgrowth alone but does appear to change the morphology of PC12 cells in the presence of NGF.

**Abstract O95**

**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 SIGA 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 sub-population.

**Methods:** Peripheral blood samples in patients with AP were assayed for sCD14 (24 and 72hr from onset) and correlated with clinical severity (Atlanta Criteria), and SIRS (Acute Physiology Score, AP). 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 67µg/L [R:25–216]) compared to mild attacks (n=70) (median:50µg/L [R:24–103], p<0.001), and healthy controls (n=40) (median:51µg/L [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 increased in severe attacks (p<0.05), 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 predetermined.

**Abstract O96**

**INTESTINAL DENDRITIC CELLS INCREASE T CELL EXPRESSION OF α4β7 INTEGRIN**

A.J. Stagg1, M.A. Kammi2, S.C. Knight1. 1Antigen Presentation Research Group, Imperial College at Northwick Park; 2St Mark’s Hospital, London, UK

Integrin α4β7 binds to MadCAM-1 and contributes to homing of lymphocytes to mucosal tissues. Monoclonal antibodies to α4β7 mediate a rat inflammatory response at the time of surgery in patients with OJ.

**Results:** Severe AP (n=20) was associated with an early sustained increase in plasma sCD14 (median 67µg/L [R:25–216]) compared to mild attacks (n=70) (median:50µg/L [R:24–103], p<0.001), and healthy controls (n=40) (median:51µg/L [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 increased in severe attacks (p<0.05), 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 predetermined.

**Conclusion:** These observations support the hypothesis that enterotoxins have a direct effect on neuronal cells. CT and LT induce neurite outgrowth in PC12 cells and enhance the neuronal differentiation effects of NGF. StA does not induce neurite outgrowth alone but does appear to change the morphology of PC12 cells in the presence of NGF.

**Conclusion:** These observations support the hypothesis that enterotoxins have a direct effect on neuronal cells. CT and LT induce neurite outgrowth in PC12 cells and enhance the neuronal differentiation effects of NGF. StA does not induce neurite outgrowth alone but does appear not to be genetically predetermined.
Results: Almost all mouse T cells freshly isolated from mesenteric (MLN) and peripheral (P LN-axillary, brachial and inguinal) nodes stained weakly for α4β7 but a subpopulation became α4β7+ upon activation with anti-CD3 in a cell cycle- and accessory cell-dependent manner. Precursor frequency analysis revealed that a small proportion (1.6±0.3%) 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 via the activating DC may be useful in therapy of intestinal inflammation and development of mucosal vaccines.

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 reduced sensitivity to steroids when measured in vitro. Interleukin-2 (IL2) is released by activated T lymphocytes and acts as a natural steroid antagonist, promoting proliferation and reducing apoptosis. 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 (Imax). Imax was measured in the absence and presence of BAS (1 mg/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 (Imax<60%) were modulated (in vitro) to steroid-sensitive by the addition of BAS.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Interquartile range</th>
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<tr>
<td>Dexamethasone</td>
<td>78.0</td>
</tr>
<tr>
<td>Dexamethasone + Basiliximab</td>
<td>92.3</td>
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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 adjuvant therapy in steroid-resistant subjects. A clinical trial of basiliximab in steroid-resistant UC is planned.

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 lysozyme, 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 CD 68.

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 pneumoniae intestinalis. TNFα expression was also noted in Paneth cells, epithelial cells and circulating macrophages and correlated with the histological severity of NEC. Lysozyme 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.

A Pro-Inflammatory Cytokine Cocktail Increases CCK Release from STC-1 Cells via an Effect on Intracellular Calcium

F.C. Leslie, T.J. McLaughlin, S. Kazmi, A. Varro, G. Warhurst, G.J. Dockray, G. Thompson. GI Science and Gut Barrier Group, Hope Hospital, Manchester; 2Physiological Laboratory, University of Liverpool, UK

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+]i), changes in [Ca2+]i, in response to 70 mM 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 38.8±4.6% increase in CCK secretion compared to control (p=0.002), IL-1β (0.125ng/ml) produced a 16.9±1.5% increase (p=0.005) and TNF-α (5ng/ml) produced a 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+]i, but pre-incubation for 2 hours produced a 23.9±2.9% (p=0.03) increase in the [Ca2+]i 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 DDF.
**FUNCTIONAL IL-18 RECEPTOR EXPRESSION BY HUMAN INTESTINAL EPITHELIAL CELLS REQUIRED FOR INHIBITION OF CRYPTOSPORIDIUM PARVUM DEVELOPMENT BY IL-18**

R.C.G. Pollok, V. McDonald, M.J.G. Farthing, M. Bajaj-Elliott. St Bartholomew’s & The Royal London School of Medicine and Dentistry; University of Glasgow

**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 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 the cells. Restriction digests confirmed 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. Since 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 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 15–45/10⁶ PBMC. In addition, 11 (69%) patients presented CTL reactive with the Influenza A peptide and 9 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 might be recruited 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, Ga1β3GalNAcα.

**Data presented as number of cases from each group positive for any bacterial growth. Significant difference from normal, *p<0.004, †p=0.044.**

**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-adhesin-positive 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.

**Conclusions:** 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 4 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 baker’s yeast (Saccharomyces cerevisiae). The epitope for this antibody is oligomannan which is present in bacterial and yeast cell walls. Our hypothesis is that oligomannan, shed by intramuscular bacteria, may inhibit neutrophil and macrophage function within the mucosa, leading to the granulomatous lesions seen in CD.

**Methods:** The effect of S. cereviseae 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 luminol dependent chemiluminescence by 68% (±5%, n=6). Luminol 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 isoluminol and cytochrome c reduction largely measure extracellular superoxide secretion, the oligomannan may have an effect on NADPH oxidase activity.

![Oligomannan decreases the neutrophil respiratory burst](http://www.gutjnl.com)

**Conclusion:** S. cereviseae oligomannan causes dose-related inhibition of the PMA-induced respiratory burst. It has extracellular and probably intracellular effects. This supports the hypothesis that microbial oligmannans 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 (0–118), P=0.002) 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 viral vectors encoding 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 immunomodulatory effects and to assess its therapeutic efficacy in IL-10 -/- mice with established colitis.

Results: A single rectal infusion of 5x10^9 PFU AdvmuIL-10 to 10 week IL-10 -/- mice induced a median of 27.3 pg/ml 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 5x10^9 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-1β over the four-week experiments was 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-α 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 replicated 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 (-1031A, -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 electrophoretic mobility shift assays; in vitro GST pull-down assays of transcription factors OCT1, NF-KB, and deletion mutants; in vitro COS cell immune-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 IBD=90.9% (n=587 unrelated cases, P=0.001 vs HC 83.1%), NOD2 cases CD=92.1%, UC=92.1% (n=241, P=0.001, UC=92.1%, P=0.008). Higher stimulated TNF production was seen in whole blood from TNF-857C homozygotes (P=0.03) at 2 hours. The OCT1 transcription factor bound the TNF-857T but not the TNF-857C allele, adjacent to a NF-KB site. The DNA binding domains of OCT1 and NF-KB p65 interacted in vitro and in vivo. OCT1 diminished NF-KB induced reporter gene expression.

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.

INTERLEUKIN 10 SECRETION DIFFERENTIATES BETWEEN INTERSTITIAL DENDRITIC CELLS FROM HUMAN LIVER AND SKIN

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Dendritic cells are thought to be the only cell capable of initiating primary immune responses, to produce both immunity and tolerance. They are also able to direct the kind of T cell response generated to specific antigen. Liver immune responses are relatively weak, not even liver allografts are less susceptible to rejection. Human liver dendritic cells (DCs), which may orchestrate the liver’s unique immunoregulatory functions, remain poorly characterised. We used a novel technique of overnight migration from tissue pieces of normal liver and skin to obtain human tissue-derived DCs with minimal manipulation and no additional cytokine treatment.

As presented at a previous BSG liver DCs have a monocyte-like morphology and a partially mature phenotype after migration overnight from tissue. We now show that liver DCs express CD123, a marker expressed by a subset of DCs associated with initiating Th2 T cell responses. In addition, a functional comparison was made between liver and skin DCs isolated the same way. ELISA measurement of cytokine in DC conditioned media showed that liver DCs produced IL-10 whereas skin DCs failed to secrete IL-10 even after stimulation and neither skin nor liver-dervied DCs secreted IL-12. The effect of DC stimulation on T cells was studied following coculture and T cell intracellular cytokine staining. Liver DCs stimulated T cells to secrete IL-10 whereas skin DCs stimulated IFNγ and IL-4 secretion in the absence of detectable IL-12.

We show for the first time clear tissue-specific differences in human non-lymphoid DCs. The ability of liver DCs to secrete IL-10, a cytokine implicated in down-regulation of immune responses, may explain how interstitial DCs from normal liver can maintain tolerance to gut derived Ag, by controlling the type of response generated in tissue or draining lymph node.

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 = 0.001). 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

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are currently being undertaken to address the possible functional effects of this polymorphism.

110 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 reflex; 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 (AHH) (disease controls). All had had >1 male child and none met ARA criteria for scleroderma or had had a blood transfusion or a liver transplant when pregnant.

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

<table>
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<tr>
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<th>0</th>
<th>1</th>
<th>&gt;2</th>
<th>x^2 chi2</th>
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<tbody>
<tr>
<td>Blood</td>
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<tr>
<td>PBC</td>
<td>27(49)</td>
<td>19(35)</td>
<td>9(16)</td>
<td>9.86</td>
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<tr>
<td>Normal</td>
<td>13(27)</td>
<td>15(31)</td>
<td>21(43)</td>
<td></td>
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<tr>
<td>Liver</td>
<td>1(2)</td>
<td>10(24)</td>
<td>31(74)</td>
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<tr>
<td>AHH</td>
<td>3(14)</td>
<td>7(33)</td>
<td>11(52)</td>
<td>(&lt;0.02)</td>
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</tbody>
</table>

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.

111 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. 31,32 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 31,32 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 +/- 1.15 mU/l, p<0.0014 and higher 31,32 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 31,32 split proinsulin levels and insulin resistance. Patients with NAFL are at increased risk of developing T2DM. Measurement of 31,32 split proinsulin may help to select individuals with higher 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 overproduction of glucose through mechanisms that are incompletely understood.

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

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Introduction: The activated hepatic stellate cell (HSC) is central to liver fibroin 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 in the liver. This, together with the observation that the T2G mutant inhibited TIMP-1 expression as well as TIMP-2, correlated with loss of TIMP-1 expression as well as TIMP-2, correlated with loss of TIMP-1 expression in noninnflamed liver fibrosis with persistent TIMP-1 mRNA expression. After induction of fibrosis in vivo, TIMP-1 knockout mice demonstrated significantly more HSC apoptosis relative to wild type animals 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.

113 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.

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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 the 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.

**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 main 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 nitrite [the end product of nitric oxide, (nO)] 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 (94.1 ± 11.03 µmol/L) in cirrhotic patients were significantly (P < 0.05) increased by comparison to the control (36.6 ± 11.03 µmol/L). iNOS was completely absent from the control group but was highly expressed in the liver of the cirrhotic group. ecNOS was seen mainly in the inflammatory cells infiltrating the portal tracts, blood monocytes, hepatocytes, sinusoidal cells and vascular endothelial lining. However, ecNOS 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.

**Splanchnic Vascular Hyporeactivity in Human Cirrhosis is Related to Disease Severity and Mediated 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 vasoconstrictors and splanchic vasodilatation. The effect of disease severity on intra vascular reactivity and the mechanisms involved in humans have not been studied.

**Methods:** We studied endothelial-denuded rings of human hepatic artery from patients undergoing orthotopic liver transplant for cirrhosis (n=9) 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). 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 LNMMA 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.

**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 hepatic adhesion/cell death.

**Methods and Results:** HepG2 cells were cultured in media supplemented with 10/20% ALF or Normal human (NS) serum. Cultures 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, a, α) 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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<table>
<thead>
<tr>
<th>Culture duration</th>
<th>20% Normal serum (NS)</th>
<th>20% ALF serum (ALF)</th>
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<tbody>
<tr>
<td>4 hours</td>
<td>86.3 +/- 7.5</td>
<td>48.3 +/- 7.7</td>
</tr>
<tr>
<td>24 hours</td>
<td>93.5 +/- 14.8</td>
<td>46.5 +/- 7.6</td>
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<tr>
<td>48 hours</td>
<td>80.3 +/- 11.3</td>
<td>30.3 +/- 7.6</td>
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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?


Prognostic 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 Progression to FHF. The equation derived by linear regression to relate the two values is Manchester prothrombin time = 0.61 + (1.72 x Innovin prothrombin time) [R²=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 shorter 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 patient had an Innovin PT of greater than 100 seconds, which is one of the requirements for consideration of liver transplantation for paracetamol poisoning. A time of 28.7 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 is known to improve survival in severe 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 subsequently 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 demographical 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 duration of hospitalisation in the two groups were not statistically significant. Serum alkaline phosphatase and bilirubin in the two groups were significantly different. PTX was well tolerated in all the patients and all received 4 weeks therapy. 3 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. Further randomised trials are clearly needed to verify these preliminary data.

[119] ACUTE SICKLE CELL HEPATOPATHY: A NEW CONTRAINDICATION 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) and sickle cell disease, 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, post-biopsy reports, and the Cornrow’s death register were reviewed.

Results: Demographics, duration of disease, frequency of sickness 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. No patient with sickle cell disease, who underwent biopsy, died. Of the 16 biopsies, 50 and 100 seconds as measured by the Manchester method.

Conclusions: Percutaneous liver biopsy in patients with acute sickle cell hepatopathy complicating sickle cell anaemia carries a high risk. To recognise acute sickle cell hepatopathy 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 respectively. 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)
pulmonary embolism and one blocked front endoscope lens which required repair. The re-bleed rate was 35% (TIPS) vs 40% (glue) (p=0.53). The inpatient stay was shorter in the glue group (18±2 vs 18±2, p=0.05), but there was no difference in the early mortality rate (17% vs 15%). The median cost within six months of initial GV bleeding was £2685 (1924–5717) for glue vs. £8211 (5517–12,001) for TIPS (p=0.001).

Conclusion: In this comparable group of patients, histoacryl glue injection is more cost effective than TIPS in managing acute GV bleeding. A prospective, randomised trial is required to substantiate our analysis.

**GENETIC HAEMOCROMATOSIS (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 (GGHB) area homozygous for the C282Y mutation up to 1 August 2000 were identified. The prevalence of GH was estimated from the frequency of GH in controls and the known GGHB 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 7. An estimated 1 in 183 (5.5 per 1000) were homozygous, which equates to 4942 cases of GH within the 904,400 population of the GGHB area. Only 240 (0.26 per 1000) C282Y homozygotes are estimated to be living in the Greater Glasgow Health Board area homozygous for the C282Y mutation up to 1 August 2001 were identified. The prevalence of GH was estimated from the frequency of GH in controls and the known GGHB population. The number of patients with undiagnosed GH was estimated from this figure and the number of known cases of GH.

**Conclusion:** As expected the C282Y mutation frequency is high in 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 penetration 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 310 IVDU (63%) and 85 blood products (17%). Primary reasons for not receiving therapy: 105 (33%) 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.

Only 37% of HCV patients attending our clinic received anti-viral therapy. The major reasons for non-treatment were related to inadequate evaluation 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 HEART DISEASE RISK AFTER LIVER TRANSPLANTATION**

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**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 (<0.001). Hypercholesterolaemia was present in 16 % before and 60 % after transplant (<0.001). 29 % were overweight at the time of transplant compared with 38 % after transplant (<0.001). Diabetes mellitus was present in 8 % before and 12 % of patients after transplant. There were 3 non-fatal cardiovascular events: 1 myocardial infarct, 1 heart failure and 1 cerebellar infarct. The Joint British Societies Coronary Risk Prediction Charts category 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 reducing 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 PERICRYPTAL MYOFIBROBLASTS IN THE MOUSE AND HUMAN SMALL INTESTINE AND COLON

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Background: The intestinal sub-epithelial myofibroblasts (ISMF) 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 ISMF might be from the neural crest, or locally from mesenchymal stem cells situated 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) gut interstitial cells of patients that had received 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 1.4 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 donor (bone marrow) origin.

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

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

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Background: The gastric enterochromaffin-like cell has recently been shown to be under the influence of neural pituitary adenylate cyclase-activating polypeptide (PACAP). Its histidine decarboxylase gene promoter is known to be regulated by gastrin, and we have explored the role of PACAP in this regulatory pathway.

Methods: A cancer gene array was probed with samples from AGS-cells expressing the gastrin-CCKB receptor stimulated with gastrin. The expression of gastrin-regulated genes was characterized 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 unidentified, 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±0.3ng/ml, n = 9; multiple endocrine neoplasia type 1 (MEN-1): gastrin, 0.53±0.09 nM, PAI-2, 2.02±0.2 ng/ml, n = 10; gastrinoma: gastrin, 0.03±0.01 nM; PAI-2, 0.66±0.2ng/ml, n = 9). More recently, 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 transfected AGS cells with 2.34kb 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.

126 PARACRINE COX-2-MEDIATED SIGNALLING BY MACROPHAGES PROMOTES TUMORIGENIC PROGRESSION OF INTESTINAL EPITHELIAL CELLS.

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Cyclooxygenase-2 (Cox-2) plays an important role during the early stages of intestinal tumorigenesis. Cox-2 is expressed predominantly by stromal macrophages in murine and human intestinal adenomas. This implies the existence of paracrine COX-2-mediated signalling between stromal macrophages and intestinal epithelial cells.

In vitro models were developed incorporating a murine macrophage cell line (RAW264.7) and a non-transformed rat intestinal epithelial cell line (IEC-6). Functional Cox-2 expression was up-regulated in RAW264.7 cells activated by interferon and lipopolysaccharide. The effect of activated RAW264.7 cells on IEC-6 cell phenotype was tested in macrophage-conditioned medium (MCM) and co-culture experiments.

In the presence of activated MCM (AMCM), IEC-6 cells reproducibly (n=5) developed ‘fibroblastoid’ morphology with decreased contact inhibition and cell overgrowth. Similar findings were demonstrated using the co-culture model. AMCM-cultured IEC-6 cells developed a stable, homogeneous ‘transformed’ phenotype by approximately 60 days. Incubation with non-activated MCM (NMCM)
was not associated with significant changes compared with control IEC-6 cells. AMCM-cultured IEC-6 cells maintained cytokinin expression but expressed decreased membranous E-cadherin, decreased TGFβRII (associated with resistance to TGFβ1) and increased Cox-2 as well as PAI-1 compared with control and NCMMC-cultured IEC-6 cells. AMCM-cultured IEC-6 cells exhibited anchorage-independent growth in soft agarose basement membrane matrix 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 AMCM-cultured 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-TERNALLY TRUNCATED CYTOPLASMIC FORM OF OXYGEN-REGULATED PROTEIN 150 (ORP150), THE MAJOR INTRACELLULAR LIGAND FOR THE ANF/PROLIFERATIVE MUSHROOM LECTIN, IS ESSENTIAL FOR NUCLEAR LOCALISATION SEQUENCE (NLS)-DEPENDENT NUCLEAR PROTEIN IMPORT IN HUMAN INTESTINAL CANCER CELLS

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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 interaction 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 a N-terminally truncated cytoplasmic form of Orp150 (Gastroenterology 2001;120(suppl 1):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 immunosorption 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 Ras-associated proteins (RanBP1, RCC1, RanGAP1 and NTF2).

This result suggests that the truncated cytoplasmic 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 (HPP) this occurs by microsatellite instability (MSI) and chromosomal instability (CI). In sporadic CRC, the serrated CRC pathway has been suggested to lead to proximal CRC with high levels of microsatellite instability (MSI-H).

Aims: To investigate the heterogeneity of MSI and K-ras and p53 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).

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 SAAs showed accumulation of mutant p53. Neither of the two HP/SAs 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 late event. MSI was rare in this predominately distal tumour series.

TELOMERE EXPRESSION IN BARRETT’S, OEOSOPHAGEAL 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 adenocarcinomas. In hyperplastic polyposis (HPP) this occurs by microsatellite instability (MSI) and chromosomal instability (CI). In sporadic CRC, the serrated CRC pathway has been suggested to lead to proximal CRC with high levels of microsatellite instability (MSI-H).

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) adenocarcinomas 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

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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 oesophageal metaplasia and examined 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-xB activation.

In summary TNF-α is up regulated in the progression of Barrett’s Esophagus. 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

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Background: The development of oesophageal adenocarcinoma is characterised by progression along the Barrett’s metaplasia – dysplasia – carcinoma sequence. It is known that the growth factor TGFα 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, Barrett’s metaplasia, dysplastic Barrett’s and oesophageal adenocarcinoma. Staining was scored semi-quantitatively. Western blotting was carried out on biopsy samples of normal oesophagus, Barrett’s metaplasia and oesophageal adenocarcinoma.

Results: Up-regulation of met was seen along the sequence with strong membranous staining seen in 0/10 normal oesophagus, 4/10 Barrett’s, 5/10 dysplasias and 7/10 carcinomas. Src is ubiquitously expressed but strong membranous staining was seen in only 3/10 Barrett’s and 6/10 carcinomas. ErbB2 showed reduced expression in Barrett’s 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 appear 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 signalling, 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

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Background: Oesophagitis has a Th1 cytokine profile in contrast to the Th2 profile (IL-4, IL-10) with low levels of TGFB-1 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: 1. 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), Barrett’s (BO=50), non-dysplastic BO (n=50), and Barrett’s adenocarcinoma (AC, n=5).

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

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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 (NO3−), derived from dietary nitrate (NO2−), 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 microfluidics probes to simultaneously measure the concentrations relevant to nitrosation in the oesophagus, cardia, proximal stomach and distal stomach of 15 healthy volunteers before and after ingestion of 2mlm of nitrate (equivalent to a salad portion).

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

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

Abstract 134

<table>
<thead>
<tr>
<th>Saliva</th>
<th>Distal Oeso</th>
<th>Gastric cardia</th>
<th>Proximal stomach</th>
<th>Distal stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN[μM]</td>
<td>1378</td>
<td>629</td>
<td>469</td>
<td>651</td>
</tr>
<tr>
<td>NO2[μM]</td>
<td>215</td>
<td>166</td>
<td>20.5*</td>
<td>0</td>
</tr>
<tr>
<td>AA [μM]</td>
<td></td>
<td>7.4</td>
<td>7.8*</td>
<td>19.9</td>
</tr>
<tr>
<td>NO/AA</td>
<td>ratio</td>
<td>18.5</td>
<td>2.7*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*p<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.

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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, but 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 floaters 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 COX-2 inhibitor, has an even greater inhibitory effect on these cells, and is a potent inducer of apoptosis and cell-cycle arrest.

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 (Miyazaki et al, 1999). The aim of these studies was to determine whether gastrin modifies endotelial vessel formation of human umbilical vein endothelial (HUVEC) cells in 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 (n=2 wells 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 using 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 (2.3)</td>
<td>p=0.00005, p=0.0005</td>
</tr>
<tr>
<td>Suramin</td>
<td>5.9 (0.5)</td>
<td>p=0.00005, p=0.0005</td>
</tr>
<tr>
<td>VEGF</td>
<td>29.5 (2.8)</td>
<td>p=0.00005, p=0.0005</td>
</tr>
<tr>
<td>G17</td>
<td>30.0 (2.0)</td>
<td>p=0.00005, p=0.0005</td>
</tr>
<tr>
<td>GlyG17</td>
<td>31.0 (1.7)</td>
<td>p=0.00005, p=0.0005</td>
</tr>
</tbody>
</table>

Conclusion: G17 and GlyG17 are able to induce an angiogenic response in HUVEC cells which is equal in magnitude to that induced with VEGF.

137 GASTRIC ADENOMATOUS POLYPS DEMONSTRATE ACCUMULATION OF MUTANT P53

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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 adenoma (Dako) were used. 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, compared with none of the control specimens (see table 1).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal (15)</th>
<th>Gastric cancer (15)</th>
<th>Gastric adenoma (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutant P53 positive</td>
<td>0 (0%)</td>
<td>6 (40%)</td>
<td>15 (100%)</td>
</tr>
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</table>

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 closely with sections that were stained in the adenoma-carcinoma pathway in the colon than the more common metaplasia-dysplasia-carcinoma pathway that occurs in the stomach.

138 DETECTION OF TELOMERASE ACTIVITY IN CIRCULATING COLORECTAL TUMOUR CELLS

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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 TelTAGG 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
Correlation between uptake of labelled colonoscopy induced pain: nurses are better intercollegiate

Background: It has been reported that administration of an anti-CCK-BR / 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/PF.1/S (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 stained 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.

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

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Introduction: Colonoscopy may be complicated by bleeding, perforation 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 events 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 advice prior to colonoscopy. Contrary to the GMC advice, patients are frequently consented in the procedure room. 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

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

Methods: We conducted a prospective study of 474 colonoscopies performed most of which were performed by 5 endoscopists. Agreement for colonoscopy 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 1.1), 3.09 (S.E.0 1.1) and 3.2 (S.E.0 1.3) 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 may 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.

142 DO ALARM SYMPTOMS IN DYSPHASIC PATIENTS WARRANT URGENT UPPER GI ENDOSCOPY?

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Introduction: Direct access endoscopy referral forms have been used by local GP’s for 2 years. The local Dyspepsia Management Guideline recommends urgent referral for dyspeptic patients with dysphagia, weight loss, anaemia, recurrent vomiting. There is little evidence to support the value of these symptoms in predicting serious pathology. We reviewed the outcomes of patients referred with alarm symptoms in our population.

Methods: A 12 month retrospective study was performed (Sept 00 - Aug 01). Endoscopy lists, referral forms and outcomes were obtained from centralised records. Pathology records of all upper GI cancers presenting in study period were collected.

Results: 597 GP referrals were endoscoped. 274 (46%) had alarm symptoms; mean age 58 (19–87). Symptom frequencies were dysphagia 32%, wt loss 50%, anaemia 14%, vomiting 35%. In those with alarm symptoms, 88 had a normal endoscopy, 99 had some gastritis/denuditis, 39 had oesophagitis alone, 20 had peptic ulcer, 5 (1.8%) gastric cancer, 7 (2.5%) oesophageal cancer, 9 (3%) had Barretts. None of the alarm symptoms were predictive of a particular diagnosis. Over the study period, a total of 67 upper GI cancers presented to the hospital (28 oesophageal, 32 gastric, 2 duodenal, 3
SEDATION FOR COLONOSCOPY: A RANDOMISED, CONTROLLED TRIAL COMPARING PATIENT-CONTROLLED ADMINISTRATION OF PROPOFOL AND ALFENTANIL WITH PHYSICIAN-ADMINISTERED MIDAZOLAM AND PETHIDINE

C. Rosevare1, L. Bright1, D. Dalgleish1, J. Kimble, H. Shepherd. 1Southampton 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 set up 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 endoscopy nurse without causing significant delay. Patients in the PCS group recovered significantly faster (35mins vs 75mins, p<0.0001) and left the endoscopy department much sooner (mean 5mins vs 14mins, p=0.01). Satisfaction scores were equal in the two groups.

Conclusions: In our population, alarm symptoms in young dyspeptic patients rarely indicated upper GI cancer. The cancers arose in older subjects. Those who were referred urgently had a significantly greater chance of attempted curative surgery. Rapid assessment of dyspepsia patients with alarm symptoms should therefore focus on older patients. In this study, all patients with alarm symptoms aged less than 55 could have been managed empirically with a ‘test and treat’ +/- PPI policy.

THE VARIABLE STIFFNESS COLONOSCOPE: ASSESSMENT OF EFFICACY BY MAGNETIC ENDOSCOPE IMAGING


Background: Variable-stiffness colonoscopes (VS scope) combine paediatric flexibility shaft characteristics for negotiation of the sigmoid colon with the ability to stiffen to prevent looping and facilitate straightening. Previous studies have shown a wide variation in efficacy of the stiffening mechanism, based on subjective assessments and differences in methodology. Two studies were conducted to assess the potential benefit of the stiffening device and its optimal use.

Methods: In study 1, the effect of routinely stiffening the straightened VS scope (Olympus CFQ240AL) in the mid-descending colon was determined in 82 patients. Two insertions were performed in each patient, from the mid-descending colon to caecal pole, with and without application of the stiffening device (randomised). The time taken to negotiate the proximal colon (from the mid-descending to caecal pole), time to pass the scope across the splenic flexure into the transverse colon, time to pass the right colon, and ancillary manoeuvres used were recorded for each insertion. In study 2, consecutive patients, excluding any with previous colonic resection, were examined using standard adult variable-stiffness colonoscopes. Real-time views of the procedure using magnetic endoscope imaging (MEI) were recorded in all examinations, but procedures were randomised to be done either with (n=88), or without the endoscopist viewing (n=87) the MEI display. Whenever shaft stiffening was applied, the anatomical location of the colonoscope tip and stiffness efficacy was recorded.

Results: Study 1—Time taken to negotiate the proximal colon (p=0.0041) and time to negotiate the splenic flexure (p=0.006) were significantly shorter and ancillary manoeuvres performed were fewer when using MEI (p=0.0014), when insertion was carried out with the stiffening device activated. Study 2—Shaft stiffening was used with similar frequency in patients examined with and without the MEI view, most commonly for passing the splenic flexure (71%), but also in the transverse colon (12%), right colon (9%) and sigmoid/descending colon (8%). Shaft stiffening was significantly more effective when used in combination with MEI (69% with imager vs. 45% without imager; p=0.0102).

Conclusions: Overall, the variable-stiffness device was effective in combination in 57% of the time. Activating maximum shaft stiffness appears to be most effective once the sigmoid colon has been negotiated and the scope straightened with the tip in the proximal colon, reducing the number of ancillary manoeuvres and shortening the insertion time through the proximal colon. Routine colonoscopy imaging with MEI further enhances the efficacy of VS scopes by helping to identify the optimal time for scope stiffening.
THE EFFECT OF TEMPERATURE ON THE FLEXURAL RIGIDITY OF VARIOUS COMMERCIALLY AVAILABLE COLONOSCOPE AND GASTROSCOPES

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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 °C compared with room temperature.

Methods and Results: We measured EI in a range of different Olympus and Pentax colonoscopes and gastroscopes (n=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 flaccid 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. Broker, 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 interpretation of withdrawal and torqueing manoeuvres, essential to achieving colonoscopy. 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 °C compared with room temperature.

Methods and Results: We measured EI in a range of different Olympus and Pentax colonoscopes and gastroscopes (n=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 flaccid 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.

ARGON PLASMA COAGULATION: AS EFFECTIVE AS “HOT-BIOPSY” FOR DESTROYING SMALL ADENOMAS. A RANDOMISED CONTROLLED STUDY

J.C. Broker, 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 outpatients 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 polyt 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 system. This could offer a safe and efficient alternative to traditional “hot-biopsy”.

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Clinical studies of wireless capsule colonoscopy

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Background: Wireless capsule endoscopy has the potential to deliver video images from 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-pig with 4 silver-oxide batteries and a potential transmission time of 18 hours were used in 7 lids. Lighter capsules (n=3) were used in 12 of 17 capsules with two batteries and a 2 hour rest period moving with the fluid phase were tested. 2 capsules were placed retrograde 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 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 light were tested and occasionally imaged the toilet. Clinical studies in 13 patients revealed missed colon cancer/polypl (3), bleeding Meckel’s diverticulum (1), ulcerative colitis (2), angiodysplasia (2). Small intestinal transit times were median (4 hr), range (1-2-7hrs). Ora-oral 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 colon 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.

Methods: 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 colon 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 immunohistochemistry 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 colon 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 in the gene level in 13 pancreatic adenocarcinomas by RT-PCR, and immunohistochemistry in 17 pancreatic tumours. Gastrin and CCK2 expression was also demonstrated in all four pancreatic tumour cell lines at the gene and protein levels by RT-PCR and western blotting. (*Student’s t-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.

Gastriazine does not inhibit the biological activity of a human pancreatic tumour growing in the pancreas of immunodeficient mice

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Introduction: Gastriazine (Gemzar), a novel nucleoside analogue, exerts its action by inhibiting DNA synthesis. Gastriazine 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 effect of gastriazine on the expression of 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 body of the pancreas in immunodeficient mice (1x10^6 in a 20µl volume). Mice were treated with saline or gastriazine 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 gastriazine 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=0.2*). Gastrin (p=0.08*), gastrin (p=0.15*), COX-2 (p=0.3*) and CCK2 receptor expression (p=0.20*) gene expression. (*Student’s t-Test.)

Conclusion: Gastriazine 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?

P.J. Arumugam, P.J. Shankar, P.N. Haray (introduced by V.I. Shah). Prince Charles Hospital, Merthyr Tydfil, Wales, UK

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


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.

Methods: 126 patients with AP (56% gallstone and 9% alcohol-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 an uncomplicated outcome. 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, 57%), 24 hr APACHE III (0.644; cutoff, 8; sensitivity, 53%; specificity, 62%; correct, 55%), 24 hr APACHE II (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

D.A.J. Lloyd, A. Tinta, A. Majeed, R.C.N. Williamson, J.D. Maxwell, J.Y. Kang, St George’s Hospital; Office of National Statistics; University College; Hammersmith Hospital, London, UK

Aim: To investigate time trends for the numbers of hospital admissions for acute and chronic pancreatitis 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 ‘Finished Consultant Episodes’, excluding day cases, in England. Hospital admissions were selected by primary diagnosis and admissions where surgical operations (excluding endoscopic procedures) were performed were identified. Age-standardised hospital admission rates were calculated using the European standard population. Mortality statistics were also obtained.

Results: Over the 11-year study period, admission rates for acute pancreatitis rose by 43% while those for chronic pancreatitis rose by 100% (see table). 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.

Methods: 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 to expected PDAC was calculated for histologically confirmed PDAC patients with at least three generations of HP. The expected PDAC was calculated for histologically confirmed PDAC in the UK and Ireland consortium of EUROPAC. We used a chi-squared test to assess for potential confounding variables.

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

AUDIT OF SECHAT TESTS: WHO TO TARGET?

B.C. McKaig, N. Simpson, I. Amarkone, R.F.A. Logan. Division of Gastroenterology, University Hospital, Nottingham NG7 2UH, UK

Introduction and Aims: To evaluate 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 (BAM)

Methods: Patients undergoing SeCHAT tests from 1994–2001 were identified and the case notes examined to verify the SeCHAT test 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 SeCHAT at 7 days 3.75%, 33.8% and 1.24%, respectively). The indication in all cases was diarrhoea. Of the 51 positive tests, 21 had previous surgery (16 terminal ileal [T] resection, choledectomy); 21 had known T1 Crohn’s disease; one had received radiotherapy involving the T; 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 T1 Crohn’s disease, previous surgery or other known predisposing factors for BAM. Prior to a positive SeCHAT test, most (90%) had...
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 Ellen syndrome and another with caudinoid 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.

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


**Background:** The aetiology of gallstones is unknown. High oestrogen levels, which are endogenous or through endogenous 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 gallstones. Whether this is an aetiological relationship remains to be established, but the findings raise intriguing questions about the role of oestrogen in gallstone formation.

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

K. Somasekar, P.J. Shanker, M.H. Lewis, M.E. Foster (introduced by P.S. Davies). Royal Glamorgan Hospital, Llantrisant, Mid Glamorgan, Wales, UK

**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.
Female to male ratio was 1.86:1. 8% were under age 35yrs, 30% age 36–55yrs, 45% age 56–75yrs and 17% over 75yrs. Most examinations were requested by surgical teams (65%) with 22% by gastroenterology, 13% by others and none by GPs.

Indications for MRCP were: (1) Possible stone in CBD in 44 (73%) as suggested by pain, acute pancreatitis, bout of jaundice, abnormal biochemistry or dilated common bile duct on ultrasound; (2) Pain post cholecystectomy (9%; 15%); (3) Failed ERCP (4%; 7%); (4) Unexplained jaundice (2%; 3%); (5) Possible bile leak post cholecystectomy (1%; 2%).

In only six of the 60 cases was ERCP necessary after MRCP (10%). In 90% of patients who underwent MRCP, ERCP was therefore 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%).

**Conclusion:** (1) There is a high demand for MRCP in a large district hospital. (2) Most MRCP is requested by general surgeons to exclude a CBD stone prior to cholecystectomy. (3) MRCP reduces demand for ERCP and its complications by approx 40%. (4) MRCP should be readily available in all large hospitals.

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**FURTHER EXPERIENCE WITH SPIRAL CT CHOLANGIOGRAPHY IN PATIENTS WITH BILIARY SYMPTOMS POST CHOLECYSTECTOMY**

A.C. Ashdown, I.D. Morrison, A.F. Muller. Kent and Canterbury Hospital, UK

**Introduction:** Because of the recognised complications associated with ERCP, it is valuable to diagnose choledocholithiasis 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 pts 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, in whom ERCP was not thought to be immediately indicated gave informed consent to sCTC. All had an abdominal US performed by an experienced ultrasonographer or consultant radiologist and liver function tests (LFTs) measured. This was followed by a sCTC using a Toshiba Asteion C.T. scanner, capable of 1 rotation every 0.75 seconds. At sCTC 15 pts had a CBD >/= 6mm and stones were detected in 13. 2 pts with a 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 the sCTC findings (3 small diameter stones) not confirmed, at ERCP, though 3 months later. Stones not detected by US measured 2-4 and 15 mm at sCTC.

**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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**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 history & any other information available.

**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), Olsalazine 3(1), Pantusa 12(2), Sulphasalazine 13(8). The BSG reported 6 pts needing dialysis & 7 a renal transplant. The RA reported medicolegal action in 4 cases.

All 5-ASA's may cause severe nephrotoxicity, which at best may only be partially reversible. Most cases occurred with Asacol, many after more than 12 months of therapy. The BSG Research Unit is collecting prospective data that may help in determining associated factors and whether nephrotoxicity can be avoided by frequent monitoring.

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**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
Reduced Pallidal Magnetisation Transfer Eradication of and Controls in the WM or Subcortical MTRs or in the Hypothesis that a CNS Abnormality Related to Cholestasis, Rather Than Fatigue Is the Commonest Symptom in Primary Biliary Cirrhosis (PBC), Achieve This Patient Awareness Must Also Be Targeted.

Conclusion: The introduction of guidelines has resulted in a significant decrease in the time from referral to endoscopy for patients with oesophagogastric 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.

Methods: 18 women with PBC [4 stage II; mean bilirubin 11], 4 stage III/IV [32] and 8 age-matched healthy women underwent cerebral MRS and proton spectroscopy (1H MRS). Magnetisation transfer ratios (MTR) for white matter (WM) and 4 subcortical structures were calculated and 'H MRK) of 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 'H 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 stage III-IV patients also had reduced PAL/WM ratios, although they were not statistically different from the stage I-II 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.

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</table>

Values are medians [quartiles], *significant versus pre at p<0.03.
Summary: Eradication of H. pylori infection at time of stopping PPI therapy unearths marked rebound acid hypersecretion which persists for at least 6 weeks. Rebound acid hypersecretion following PPI is not seen in those remaining H. pylori positive.

Conclusion: This acid hypersecretion induced by H. pylori eradication in patients previously receiving PPI therapy may explain the relation between H. pylori eradication and development of GERD.

Plenary posters 168–197

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 is a new treatment for refractory and fistulating 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 out patient 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.

<table>
<thead>
<tr>
<th></th>
<th>Before Infliximab</th>
<th>After Infliximab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clinic visits</td>
<td>3 (0–7)</td>
<td>2.5 (0–8)</td>
<td>&lt;0.7</td>
</tr>
<tr>
<td>Number admitted</td>
<td>13/30</td>
<td>11/30</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Total admission days</td>
<td>0 (0–80)</td>
<td>0 (0–104)</td>
<td>&lt;0.8</td>
</tr>
</tbody>
</table>

Clinic visits and admissions in the 6 months pre and post Infliximab. Data are median and ranges or frequencies.

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 hospital attendance are not to be expected with a single dose alone. 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


Ulc erative 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/G 241) and 469 (K/E 469). 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 fistulating disease and 35 non-fistulating 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 exon6 K469 was 38.2%. In CD overall, it was 76.9% (p<0.001). For CD patients with ileal disease, the frequency was 70.9% and 43.3% for non-ileal disease. For patients with fistulating disease, the K469 frequency was 69.2%, and 84.3% for non-fistulating disease. For patients with stenosing disease, the K469 frequency was 77.4%. For UC overall, the frequency of ICAM1 exon6 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 sequence of K469 to R469 of the ICAM1 molecule may influence IBD.

170 RECURRENT ORAL ULCERATION (ROU) 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 haplotypic 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 DQB1*0603 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 TEMELERASE EXPRESSION IN INFLAMMATORY BOWEL DISEASE


Background: Lymphocyte telomerase knockout mice develop ulceration and atrophy of the bowel. In humans colon neomerase 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 hTERT mRNA was quantified in about 40% of samples (18 UC, 14 CD and 14 controls) by real-time 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) < 0.0001 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 ulcerative colitis. 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 highly variable, 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) (ii) 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 colorectal adenocarcinomas, 20% showed tumour-specific mutations which were not present 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:T/A transitions at nucleotide positions 61 and 52 and one T:A/A:T transversion at nucleotide position 308. This 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 give insight into whether these mutations precede neoplasia or are a consequence of tumorigenesis.

TNM&R STAGING IN COLORECTAL CANCER: HAS THE TWO WEEK WAIT FOR PATIENTS MADE ANY DIFFERENCE?


Background: Colorectal Cancer (CRC) is the commonest cancer in the United Kingdom among non-smokers. In accordance with the Government NHS Cancer Plan, the concept of a two week wait (tww) was introduced to ensure that all patients with a suspicion of CRC were seen by a specialist within two weeks of referral. Aim: The aim of this study is to examine the effect of this implementation on tumour staging for patients with colorectal cancer. Methods: TNM staging and demographics from 140 consecutive patients diagnosed with CRC and treated at a single regional unit were collected for one year before the introduction of the tww and for a year afterwards, to September 2001. Of the 107 elective patients, 90 were operated on. 33 patients presenting as emergencies were excluded from subsequent analysis.

Results: 24/40 (60%) patients were node negative in the pre tww group compared with 32/46 (70%) in the post tww group (x²=0.21, ns). Similarly, before the introduction of the tww there were 9/40 (23%) patients regarded as being of good prognosis (T1,N0,T0,N0) or (T1,N0) compared with 13/46 (28%) in the post tww (x²=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=46) T1 =6, T2=7, T3=22 and T4=10 (x²=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=50) [median 32 & range 15–216 days] after referral (x²=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 (x²=0.19, ns). Median follow-up (days) was 535.3 (range 38–696%) & 315.5 (range 12–453.3) for pre and post tww respectively. Overall survival including emergency admissions) in the pre tww was 79.3% (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.

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

C.I. 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 resolution of acute infection. We aimed to characterise CD4 HCV specific responses in CHC patients at the start of treatment with PEG-IFN-α 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-α and Ribavirin. These cells were set up in culture with either recombinant HCV antigens or appropriate anti-viral treatment with PEG-IFN-α and Ribavirin, 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 12-453.3 based quantitation methods.

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 virological response, in which stronger responses were maintained. There were also changes in the CD4 cytokine profile induced by core and helicase recombinant proteins which correlated with virological response.

Discussion: There has been one study examining serial HCV specific CD4 responses whilst on standard combination treatment (Compay et al. 2000). Our study has similarly demonstrated that the onset of 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 APOTOPSIS IN HELICOBACTER PYLORI INFECTED MONGOLIAN GERBILS

M. Court, M.A. Aboschikawa, 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...
colonise MGs and to induce gastric pathology, gastric epithelial cell proliferation and apoptosis.

**Methods:** MGs were orally challenged three times with *H. pylori* SS1 strain. Infected animals (n=28) plus controls (n=23) were sacrificed following intraperitoneal injection with bromodeoxyuridine at 4, 12 and 36 weeks post-infection (p.i.). Gastric epithelial cell proliferation and apoptosis were determined immunohistologically and by TUNEL assay. Infection was confirmed histologically and by culture. Strains were identified as SS1 by RAPD-PCR and sequence analysis of the 16S rRNA gene.

**Results:** 27/28 of the inoculated MGs were *H. pylori* SS1 positive. At 4 weeks p.i. gastritis was antral predominant. Corpus gastritis and atrophy were present in 1/4 MGs at 12 weeks and 6/15 at 36 weeks. Gastric epithelial cell proliferation was significantly increased (p < 0.05) in the antrum of infected MGs at 12, 14 and 36 weeks p.i. At 36 weeks p.i. MGs with corpus gastritis had significantly increased corpus epithelial cell proliferation compared to uninfected controls (p < 0.005) and infected animals with no corpus gastritis (p = 0.06). *H. pylori* infection was associated with increased apoptosis in the glandular but not the superficial gastric epithelium. In the antrum epithelial apoptosis at 12 (p < 0.05) and 36 (p < 0.005) weeks p.i. was increased compared to uninfected controls. At 36 weeks p.i. a significant increase (p < 0.005) in apoptosis in the corpus glandular epithelium was evident which was restricted to the infected MGs which had developed corpus gastritis.

**Conclusions:** The SS1 *H. pylori* strain will chronically infect Mongolian gerbils resulting in gastritis by 36 weeks post infection. *H. pylori* infection is associated with increased gastric epithelial cell proliferation and apoptosis of the glandular epithelium in the antrum. Progression to corpus gastritis results in similar changes.

This study was funded by Yorkshire Cancer Research.

176 ACID LOWERS THE THRESHOLD FOR CAPSAICIN ACTIVATION OF GASTRIC MUCOSAL NEURONS

**J.I.W. Jones, D.A. Kendall, P.J. Mills, C.J. Hawkey.**

**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 neurons.

**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 gastric origin were identified by excitation of the Texas Red within them. The cells were loaded with the calcium sensitive ionophore Flura 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 10⁻⁶ to 10⁻⁴ 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 responsive cells than somatic tissue but like somatic nerves responses are enhanced at reduced pH.

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

**L.A. Haughton1, W. Atkinson1, P. Whitaker1, P.J. Whorwell1, M. Rimmer1**

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/10⁹ platelets, adjusted geometric mean) than healthy female controls (342.86ng/10⁹ 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.


178 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 (12 to date) of β-galactoside-binding lectins. It is very unclear what are the functionally important possible ligand(s) for recombinant galectin-3 in HT-29 colon cancer cells in vivo. We have used a chemical library approach to screen for putative ligands for galectin-3 in HT-29 cells. Galectin-3 is a Ca²⁺ dependent β-galactoside binding lectin which is up-regulated in invasive CRC cell lines.

**Methods and Results:** HT-29 cells were grown to 70% confluence, harvested, and a cytoplasmic extract prepared. The extract was then screened against a large range of potential ligands. MUC-1 was found to be a potentially important ligand for galectin-3.

**Conclusions:** MUC-1 is a novel ligand for galectin-3 and may be an important molecule in the invasion of human CRC.

Ferritin and TfR2 interact in small-intestinal bedside insertion of nasojejunal feeding.

Bone mineral density and mineral status of ileostomy patients.

**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 steroids. 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, Mg and Vit D status.

**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<Z-score<-2.5) and 7 (12%) had osteoporosis (Z-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 (<0.7 mmol/l) but 34 (60%) had low 24-hour urinary Mg (<3.5 mmol) 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 patients with colectomy alone are at increased risk of low BMD but this risk may be increased by additional small bowel resection and 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.

**References:**


**HFE AND TfR2 INTERACT IN SMALL-INTESTINAL CRYPT CELLS: A MECHANISM FOR IRON HOMEOSTASIS IN HEREDITARY HAEMOCROMATOSIS**

W.J.H. Griffiths, W.S. Sly, T.M. Cox. University of Cambridge Dept of Medicine, Addenbrooke’s Hospital, Cambridge; St Louis University School of Medicine, MO, USA

Transferrin receptor 2 (TfR2) is a recently-identified homologue of the ubiquitous transferrin receptor (TfR) and is expressed in the liver and small intestine. Mutations in the TfR2 gene predominate to hepatic haemochromatosis and a role for HFE in the signalling of body iron status within small-intestinal crypt cells has been proposed. TfR2 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 TfR2 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 TfR2 was observed in the crypts, where colocalisation occurred with HFE, no staining of HFE and TfR2 was observed in villus enterocytes. In contrast TfR expression, examined using a commercial murine antibody, was ubiquitous but did not colocalise with HFE. The localisation of HFE and TfR2 was further examined in situ in human Caco-2 cells, which have a small intestinal phenotype. Using confocal microscopy TfR2 stained abundantly with a vesicular pattern in undifferentiated Caco-2 cells. No colocalisation with TfR was observed by dual-label fluorescence studies confirming the specificity of the TfR2 antibody. HFE colocalised with TfR2 in an endosomal compartment following addition of iron-saturated transferrin to the culture medium.

Identification of TfR2 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 TfR2 and HFE suggests functional coupling in an endosomal transport pathway for crypt cell iron signalling.

**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 steroids. 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, Mg and Vit D status.

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**Conclusions:** Our results suggest that patients with colectomy alone are at increased risk of low BMD but this risk may be increased by additional small bowel resection and 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.

**References:**


**BEDSIDE INSERTION OF NASOJEJUNAL FEEDING TUBE: BENMARK 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 Benchmark NJT (spiral NJT) is supposed to aid post pyloric placement, but no comparative trial has been performed.

**Methods:** Patients requiring nasojejunal feeding were randomised to have either Medigrafa (straight) or Benchmark (spiral) NJT after stratification into those with or without normal gastric emptying. NJTs were placed at bedside in a standard fashion without radiological guidance by the same person (CWYL) for pre- and / or postoperative feeding. Bolus IV metoclopramide (10mg) was given prior to insertion in the abnormal gastric emptying group. Abdominal X rays were obtained at 4 and 24 hours. Successful placement was defined on X ray as passage through the duodenum from right to left, past the left border of the vertebral.

**Results:** 47 patients were randomised of which 17 (11 straight, 6 spiral) could not tolerate the NJT. Of the 30 remaining patients, 16 had normal gastric emptying. Patients having straight or spiral NJT were well matched. Successful placement of spiral NJTs was significantly more frequent with the spiral NJT (see table), mainly because of a higher success rate with the spiral NJT in the normal gastric emptying group. There was no difference in the duration of NJT in situ, complications, post-insertion hospital stay or final outcome.

**Conclusion:** Benchmark spiral NJT should be used for bedside unguided post pyloric feeding.

(We are grateful to Nutricia for supplying the Benchmark tubes.)
LONG TERM FOLLOW UP OF PATIENTS WITH GASTRIC OUTLET OBSTRUCTION RELATED TO PEP TIC ULCER DISEASE (PUD) TREATED WITH ENDS COPI C BALLOON DILATATION AND DRUG THERAPY

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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.
CURRENT ISSUES IN THE MANAGEMENT OF COLONIC NEUROLOGICAL AND COGNITIVE DYSFUNCTION IN PATIENTS TAKING ASPIRIN.

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 polypectomy 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 studied 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 53, neoplasia surveillance 387, polyps 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. 82% of advanced adenomas (size >1cm or villous histology) were proximal. Polypectomy failed to yield a specimen for analysis in 19.3% of snare 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 in this study is lower than previously reported, which may reflect improved endoscopy practice. 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 polypectomy 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 studied polyp epidemiology and polypectomy techniques and complications in patients from a single endoscopy department.

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1. V. Pollock, S. Thomas-Gibson, S.G. Shah, C.J. Thapar, B.P. Saunders. St Mark’s Hospital, Harrow, UK.

VIDEO-ASSESSMENT OF COLONOSCOPY WITHDRAWAL TECHNIQUE

J.C. Brooker, S. Thomas-Gibson, S.G. Shah, C.J. Thapar, B.P. Saunders. St Mark’s Hospital, Harrow, UK.

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 endoscopic room, was illuminated. However recording took place continuously. Extubation lists were randomly assigned to “open” 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 neoplasia surveillance. Mean (sd) time per procedure were required to improve examination quality.

Conclusions: Over 50% of extubations were sub-optimal, and awareness of video recording made no difference to quality. We suggest that better training in withdrawal technique and allotting more time per procedure are required to improve examination quality.

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.

METHOD: Patients listed for liver transplantation with no history of hepatic encephalopathy were invited to participate in the study. Standard demographic data and patient characteristics were recorded. A battery of neuropsychological tests was used to assess cognitive function and a structured neurological examination was performed. Twenty-five healthy volunteers were used as controls. The data were compared using the unpaired t-test or the Mann-Whitney U test as appropriate.

RESULTS: Twenty patients were included. The mean age was 53.25 years (sd 9.35). The median duration of illness was 60 months (iqr 6-156) and the median Childs-Pugh score was 7 (iqr 5-8). There are no significant differences in cognitive function compared to controls.
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 occurs 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 counselling of these patients and for obtaining informed consent. Current methods of monitoring cognitive impairment clinically, such as trailmaking tests, may be inadequate.

**189 A PROSPECTIVE ASSESSMENT OF HEPATIC VEIN TRANSIT TIMES USING MICROBUBBLE-ENHANCED ULTRASOUND IN NON-INVASIVE GRADING OF HEPATITIS C (HCV) RELATED LIVER DISEASE**

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**Purpose:** Non-invasive assessment of the severity of diffuse liver disease is problematic and biopsy is often needed. We evaluated an ultrasound microbubble agent and carotid-delay times (CDT) in grading diffuse liver disease in patients with chronic hepatitis C (HCV) infection using histology as the gold standard.

**Materials/Method:** 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 audio intensity from the carotid artery were analysed after an intravenous microbubble bolus. CDT was calculated as the difference between carotid and hepatic vein arrival times. Grading of fibrosis (F) and inflammatory activity (I) was carried out using the modified Ishak scoring system. Patients were divided into mild hepatitis, (F=2/6, NI≤3/18); moderate/severe hepatitis, (F=3/6, NI>4/18) and cirrhosis, (F=6).

**Results:** There was a monotonic decrease in the mean ATs ± s.d. and CDTs ± s.d. for mild, moderate/severe hepatitis and cirrhosis: 50.5s ± 24.2, 33.6s ± 26.1, 14.8s ± 4.5 and 36.8s ± 29, 18.7s ± 22.6 and 5.8s ± 4.9 respectively (Kruskal Wallis ANOVA, p<0.001). An AT>24s and CDT>10s was 100% sensitive for cirrhosis but only 69% and 72% specific respectively, as subjects with fibrosis showed similar AT and CDT. 10 interferon-treated patients showed earlier arrival times than comparative untreated subjects.

**Conclusion:** AT and CDT measurements hold promise in characterising liver disease in patients with HCV and is a highly sensitive marker of cirrhosis. Treatment with interferon appears to prolong AT. This is important for disease monitoring and may be useful in assessing the efficacy of treatment regimes non-invasively and possibly replace repeat liver biopsy in some situations.

**190 LOSS OF GLUCONEOGENTIC CAPACITY IN A FULLY ANAESTHETISED PORCINE MODEL OF PARACETAMOL INDUCED ACUTE LIVER FAILURE**


A porcine model of paracetamol induced acute liver failure has been recently developed in our laboratory. This model is suitable for pathophysiological studies in acute liver failure. As a first step we investigated the gluconeogenic capacity of the porcine liver in that particular model.

**Materials and Methods:** Thirty five kilogram large white pigs were maintained under general anaesthesia with isoflurane and nitrous oxide. Three pigs acting as controls received no paracetamol while five other pigs received paracetamol by intravenous infusion for 12 hours keeping blood levels between 200 and 300 mg/L. Blood glucose was maintained within normal limits by continuous intravenous dextrose infusion. Using 1H NMR spectroscopy we 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 euthanised.

**Results:** In control pigs there were no significant differences in the concentrations of these 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 gluconeogenic substrates studied are significantly increased whereas the end product of the pathway, glucose, is significantly decreased. This confirmed that in the model the gluconeogenic capacity of the liver is lost and further studies in humans are required to assess the observed phenomenon.

**191 GENETIC INFLUENCES IN GASTRO-OESOPHAGEAL REFUX DISEASE: A STUDY TWIN**

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**Background:** A number of family pedigrees detail multiple members with gastro-oesophageal reflux disease (GORD). Aggregation of GORD symptoms within families of patients with documented GORD has also been demonstrated. This raises the possibility of a significant genetic contribution to the aetiology of GORD. We have therefore studied GORD 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 GORD.

**Methods:** 4480 unselected twin pairs from a national volunteer twin register were asked to complete a previously validated questionnaire. GORD was defined as symptoms of heartburn or acid regurgitation at least weekly during the past year.

**Results:** 5032 respondents (56% response rate), including 1940 evaluable twin pairs. 922 MZ pairs (86 male, 836 female, median age 53(range 19–81)years) and 1018 DZ pairs (71 male, 947 female, age 54(20–82)years). The prevalence of GORD among the twins was 709/3880 (18%). Both pairwise and casewise concordance rates were significantly higher for MZ twins (see table). Heritability estimates suggest 50% (95% CI 39–61%) of the phenotypic variance in GORD is due to additive genetic factors (see table).

**Conclusion:** This study strongly suggests a substantial genetic contribution to the aetiology of GORD.

<table>
<thead>
<tr>
<th>GORD in at least one twin (pairs)</th>
<th>Concordant affected pairs</th>
<th>Discordant pairs</th>
<th>Casewise concordant</th>
</tr>
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<tbody>
<tr>
<td>MZ 257</td>
<td>71 (28%)*</td>
<td>186 (72%)</td>
<td>142/328 (43%)**</td>
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<tr>
<td>DZ 329</td>
<td>52 (16%)</td>
<td>277 (84%)</td>
<td>104/381 (27%)</td>
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<td>Total 586</td>
<td>123</td>
<td>463</td>
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</table>

*p = 0.001 versus DZ twins **p < 0.0001 versus DZ twins

**192 HEARTBURN IN PATIENTS WITH UNDIAGNOSED ACHALASIA**

S.H.C. Anderson, A. Anggiansah, M. Aratsu, R. Anggiansah, W.J. Owen. Oesophageal Laboratory, Guy’s and St Thomas’ Hospital, London, UK

**Background:** Achalasia characteristically presents with dysphagia and regurgitation. Food fermentation in the dilated oesophagus, or oesophageal distension, have been reported to cause heartburn, which may be misdiagnosed as gastroesophageal reflux disease (GORD).

**Methods:** We studied the medical notes of all patients diagnosed with achalasia in our laboratory over the past 10 years, and...
documented the onset and pattern of heartburn and other symptoms. Where available, the lower oesophageal sphincter pressure (LOSP) and pH studies were compared.

**Results:** 306 patients had a manometric diagnosis of achalasia. 81 were excluded having had a previous dilatation or surgery. Of the remaining 225, 10 (4.4%) were classified as vigorous achalasia and 5 had prior dilatation of the oesophagus. The mean duration of symptoms was 3.5 years (range 1 month to 30 years). 110 (49%) experienced heartburn, 220 (98%) had dysphagia, 131 (58%) had regurgitation, 126 (56%) had weight loss and 87 (39%) had no-oesophageal chest pain. In 54 patients (24%) the heartburn preceded the dysphagia and persisted, while in 25 patients (11%) the heartburn stopped with the onset of dysphagia. Heartburn developed after the onset of dysphagia in 46 patients (20%) and in 17 (8%) the symptoms began together.

The mean LOSP was 20.2±9.0mmHg. There was no significant difference in LOSP between these different symptom groups. 106 patients (47%) were taking anti-dyspepsia medication, 58% of these had heartburn and 53% had regurgitation. There was no correlation between the pH study and the pattern of symptoms or the LOSP.

**Conclusion:** There is a long delay in reaching a diagnosis of achalasia – up to 30 years in this study. The symptoms may not be characteristic, and weight loss, chest pain and heartburn are frequent symptoms. GORD is uncommon despite heartburn being present in half of patients. Reflux symptoms in these patients are therefore unreliable and should be investigated with a 24-hour pH study.

**193 PLASMA LEPTIN BEFORE AND AFTER CURE OF HELICOBACTER PYLORI**

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**Background:** Decreasing H. pylori prevalence has been linked with increasing incidence of oesophageal adenocarcinoma. Increasing oesophageal reflux and Barrett’s oesophagus 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 significant obesity a systemic effect should 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.

**194 PARADOXICAL DUAL EFFECT OF HELICOBACTER PYLORI ERADICATION THERAPY ON HEARTBURN AND ACID REFUX: 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 H. pylori eradication. 1634 participants had a positive 13C urea breath test, and were treated with either H. 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. A 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 severe heartburn 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.

**195 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 cholangiocarcinoma 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 from 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 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.

**196 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. Passaged rat
PSCs were used in all the experiments. PSCs were treated with NGF (1–100ng/ml) and apoptosis was assessed by nuclear morphology after cell staining with acridine orange. The proliferation rate of PSCs were determined by 3H-thymidine incorporation. Expression of p75 was assessed by Western blotting. Immunostaining of the chronic pancreatitis tissues demonstrated that p75 was positively expressed in the fibrotic bands localised in the distribution of PSCs whereas NGF was expressed in the atrophic acinar parenchyma.

Exogenous NGF(10, 100ng/ml) significantly increased apoptosis under serum-free conditions by 42±1.1% and 30±8.8% as of control. The rate of proliferation of PSCs when treated with the same concentration of NGF(10, 100ng/ml) was also reduced by 57±0.8% and 73±2% respectively as compared to control, with western blotting we demonstrated that p75 was expressed in PSCs.

We therefore conclude that the expression of p75 on PSCs and the response to NGF stimulation by apoptosis may suggest a role in recovery of pancreatic fibrosis.

**OUTCOME OF STENTING FOR NON-EXTRACTABLE COMMON BILE DUCT STONES IN ELDERLY PATIENTS: A DISTRICT GENERAL HOSPITAL EXPERIENCE OVER SEVEN YEARS**

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**Background:** Endoscopic sphincterotomy and stone extraction is an established treatment for symptomatic common bile duct (CBD) stones. Surgery is recommended when endoscopic extraction of stones fails. For elderly and/or debilitated patients who are at high surgical risk, long-term biliary stenting may have a role as a definitive therapy.

**Methods:** A retrospective analysis was conducted of all patients who had biliary stents for retained CBD stones over a 7-year period (January 1993 to December 1999). 30 patients were identified (21 women, 9 men; median age 84 years, range 49–95 years). 7/30 (23%) patients had previous cholecystectomies. Follow-up data were obtained by referral to their case notes and contacting their general practitioners.

**Results:** Successful biliary drainage was achieved in all patients. The stent was considered to be a temporary measure in 1 patient while awaiting surgery and definitive in 29. Only 1 patient had subsequent surgery (elective cholecystectomy and cholecdocholithotomy). Early complications occurred in 2 patients (6.7%); both subsequently died. Late complications occurred in 5/30 (16.7%): cholangitis 4, recurrent jaundice 1. All of these had repeat endoscopic retrograde cholangiopancreatography with successful stone extraction in 2 and re-stenting in 3. During follow-up there were 5 unrelated deaths. The remaining 17/30 (57%) were well and asymptomatic at a median follow-up period of 20 months (range 10–65 months).

**Conclusion:** Endoscopic biliary stenting for irretrievable CBD stones is an effective method of establishing bile duct drainage as definitive treatment for patients at high surgical risk.

**Biliary and pancreas posters**

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**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 re-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 73yrs, 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 23.4 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.

**EVALUATION OF LIQUID-BASED CYTOLOGY (THIN PREP) IN ENDOCOSPOIC RETROGRADE BILIARY BRUSH CYTOLOGY**

M.K. Shariff, P.A. Smith, M. Lombard, M. Punekar. University Department of Pathology and Department of Gastroenterology, Royal Liverpool University Hospital L7 8XP, UK

**Background:** Thin Prep®(Cytyc Corporation) is a liquid based cytology system prepared by an automated processor. It offers better specimen retrieval, reduces background material such as blood and polymon exudates, thus improving cytomorphology and diagnostic accuracy.

**Objectives:** (1) To compare the performance of endoscopic retrograde biliary brush cytology (EBRC) prepared by Thin Prep (TP) with directly smeared brushings. (2) To demonstrate that variability in diagnostic yield at ERBC can partly depend on the endoscopist.

**Methods:** 38 ERBC TP bile duct samples from 37 patients with biliary strictures, were compared with 36 ERBC samples from 35 patients proceed by direct smear. In addition, for the TP group, we were interested to see whether technique were consistent between four different endoscopist designated A, B, C, and D. Malignant and suspicious cytology was considered positive and benign as negative. The final diagnosis was based on histology at surgical resection and/or clinical follow up from medical records.

**Results:** 22 benign, 7 malignant, 4 suspicious, and 3 unsatisfactory results were reported on direct smear with 20 benign, 16 malignant, 2 suspicious and 0 unsatisfactory on Thin Prep. The overall sensitivity of Thin Prep for malignancy (18 of 28 positive, 64%) was significantly greater than direct smear (11 of 33 positive, 33%). The table compares the difference in sensitivity in Thin Prep group for malignant strictures with regard to different endoscopist doing the ERBC.

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<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tr>
<td>Sensitivity</td>
<td>75%</td>
<td>77%</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>Positive yield of total malignant</td>
<td>9/12</td>
<td>7/9</td>
<td>1/5</td>
<td>1/2</td>
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**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.

**LAPAROSCOPIC CHOLECYSTECTOMY RATES IN IRELAND: RECENT TRENDS**

A.N. Keeling, F.E. Murray. Department of Gastroenterology and Clinical Pharmacology, Beaumont Hospital and RCSI, Dublin, Ireland

**Background:** Studies in other countries have suggested that the overall cholecystectomy rate increased following the introduction of the laparoscopic technique in 1985.

www.gutjnl.com
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 obtained 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 old age group, with a 121% increase in the 20–24 year old 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 (3.5%), 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 indication, 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.

Conclusions: 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.

P101 PRIORITISING PATIENTS FOR CHOLECYSTECTOMY
K. Somasekar, P.J. Shanker, M.H. Lewis, M.E. Foster (introduced by P.S. Davies). Royal Glamorgan Hospital, Llantrisant, Mid Glamorgan, Wales, UK

Introduction: Emergency admission with gallstone related problems is common among patients awaiting cholecystectomy. By recognising the patients who are prone to recurrent gallstone related problems, it is possible to offer them early surgery.

Aims: To identify the risk factors associated with emergency admissions, due to recurrent gallstone related problems, in patients awaiting cholecystectomy.

Methods: A retrospective analysis was performed of all the patients who underwent elective cholecystectomy by 3 consultants in a district general hospital between 1998–2000. Patients who were admitted as an emergency while awaiting surgery were compared with the remaining patients, with regard to demographics, the specific indication for inclusion in the waiting list, the waiting time, and the ultrasound findings at the time of inclusion in the waiting list.

Results: Of the 211 patients in the study, (mean age 52 years, range 19–82 years), 58 patients (27.4 %) were admitted as an emergency with gallstone related problems while awaiting surgery (Group I). They were compared with the remaining 153 patients (Group II). The mean duration on the waiting list before the patients in Group I were admitted with recurrent symptoms was 19 weeks, as against the mean waiting time for surgery of 56 weeks in Group II patients. The mean duration of symptoms before being listed for surgery was 6.7 months in Group I, compared to 12 months in Group II. Eighteen patients were listed for surgery following an episode of acute cholecystitis in Group I, as against 15 patients in Group II (p<0.001). Ten patients in Group I had a stone in the Hartmann’s pouch on ultrasound when they were listed for surgery, compared to 6 patients in Group II (p<0.01).

Conclusions: Duration of the waiting time, by itself, may not affect the incidence of recurrent symptoms due to gallstone disease in patients awaiting cholecystectomy. Patients with symptoms of a shorter duration at the time of initial presentation to the surgeon may be at a higher risk of recurrent gallstone related problems in future. Previous acute cholecystitis and ultrasound evidence of stone in the Hartmann’s pouch are important risk factors that predict recurrent gallstone related problems in future.

202 MUCOSAL ADDRESSIN CELL-ADHESION MOLECULE-1 (MADCAM-1) AND POPOPLAIN LOCALIZATION IN PRIMARY SCLEROSING CHOLANGITIS (PSC) & PRIMARY BILIARY CIRRHOSIS (PBC)
A. Ala1, R. Standish2, K. Khan3, M. Stubbs4, K. Hillan5, A.P. Dhillon2, H.J.F. Hodgson1. 1Centre for Hepatology, 2Dept of Histopathology, Royal Free & University College Medical School, London, UK; 3Genentech Inc, San Francisco, USA

Background: MADCAM-1 is pivotal in the emigration of lymphocytes expressing α4β7 cell surface integrin from the circulation into tissues of the gut. MADCAM-1 upregulation has been demonstrated in inflammatory diseases of the liver and appears to contribute to the pathogenesis of ductopenic liver disease. We investigated the hypothesis that MADCAM-1 might play a role in lymphocyte trafficking without lymphatic vasculature in these conditions. Podoplanin is a ~38-kd membrane glycoproteins of podocytes, reported to be a selective marker of lymphatic endothelium.

Aims: We report the nature and distribution of vessels on which MADCAM-1 is expressed in cirrhotic ductopenic liver disease.

Methods: Sections of cirrhotic liver explants from nine patients with PSC and seven with PBC were evaluated for expression of MADCAM-1 & CD34 using an alkaline phosphatase immunohistochemical technique. Sections of normal liver were used as control. Podoplanin expression was evaluated by using immunoperoxidase methodology.

Results: MADCAM-1 immunoreactivity was not evident in the control liver sections, localized to lymphoid aggregates (either around the aggregate centre or in blood vessel endothelium, thought to be high endothelial venule) as well as the peribiliary capillary plexus (PBP) endothelium (associated with predominantly medium to large bile ducts). Similar staining patterns were seen in both PSC and PBC. Podoplanin was located in vessels with morphological features of lymphatic channels surrounding immediately subjacent to and separate from lymphoid aggregates. These vessels were characterised by a single layer of flattened endothelium without evidence of erythrocytes within their lumen, and were spatially distinct from vessels expressing MADCAM-1.

Conclusion: MADCAM-1 expression demonstrated within lymphoid aggregates and in PBP endothelium identifies presumptive sites of lymphocyte emigration. We have demonstrated MADCAM-1 immunoreactive in and around lymphoid aggregates, and podoplanin immunostaining shows that these vessels are not lymphatic channels. These studies suggest that the expression of MADCAM-1 on PBP endothelium may contribute to ductopenic liver disease, providing further evidence to support an immune mediated basis to the pathogenesis of PSC and PBC.

203 THE GENETIC SUSCEPTIBILITY TO NON-HEREDARY 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 increased membrane damage, protein denaturation and DNA adduction 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, GSTM-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 4HP), 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 aetiology, this association remained significant in non-alcohol related disease (p<0.05). In contrast to the data with GSTT-1, no significant association were observed between GSTP-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.

204 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 be mediated either by altered expression of anti-oxidant enzymes or depletion in cellular glutathione.

We investigated the prevalence of Ala1/Val1 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 (GST) T1-1A 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 transaminase (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 GSTT1-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). Mixed MnSOD alleles were associated with lower plasma γGT and ALP. 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.

205 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 in patients with AP of biliary origin.

In 85 patients with gallstone acute pancreatitis, blood samples taken at 24, 48, and 72 hrs from the onset of pain were analysed for ALT, γGT, and 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.

Abstract 205

<table>
<thead>
<tr>
<th>Time</th>
<th>Mild (60)</th>
<th>Severe (25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs</td>
<td>ALT 123 (15 – 1515)</td>
<td>80 (6 – 397)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>ALP 372 (86 – 1240)</td>
<td>182 (27 – 48)</td>
<td>0.007</td>
</tr>
<tr>
<td>72 hrs</td>
<td>γGT 240 (15 – 1504)</td>
<td>72 (42 – 506)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>ALT 103 (7 – 859)</td>
<td>42 (12 – 155)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>ALP 302 (108 – 184)</td>
<td>189 (21 – 515)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>γGT 196 (15 – 1515)</td>
<td>81 (6 – 397)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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.

Study design: Nineteen cases of pancreatic carcinoma treated by pancreaticoduodenectomy were studied. Tissue was received fresh and fixed in formalin for 48 hours. The head of the pancreas was serially sliced parallel to the common bile duct and blocks of the tumour were taken which included the surgical resection margins. Blocks retrieved for this study were stained using the sirius red light green method. Five images from the centre and five from the periphery of each tumour were captured using a 4x objective. An image segmentation technique based on colour cluster analysis was used to measure the fractional area of stroma, cell cytoplasm and lumen. Repeatability of the analysis technique was established previously by comparison with manual point counting.

Results: Over all 19 cases, the relative area of tissue occupied by stroma at the periphery of the tumours exceeded that at the centre by an average of 8.4 percentage points (P < 0.01). Correspondingly, the area occupied by cell cytoplasm was on average 7.8 percentage points (P < 0.01) greater at the centre than periphery. No significant difference in luminal area was observed. Measurements from multiple slices from each tumour were used to detect significant differences within individual tumours. In 9 cases, the fraction of stroma at the periphery significantly exceeded that at the centre (P < 0.05) with a mean increase in stromal fraction of 17.6% 9.4 percentage points. None of the remaining cases had significantly more stromal tissue at the centre that at the periphery.

Conclusions: The computerised image analysis technique used in this study permits colour stained tissue area to be measured rapidly. Over all tumours studied, the fractional percentage of stromal tissue was significantly greater at the periphery than at the centre. Analysis of multiple images per tumour permitted significant differences in 9 of 19 tumours to be detected.
Abstract 207

<table>
<thead>
<tr>
<th>Delay between:</th>
<th>Median (range) delay in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP referral and receipt of referral at DGH</td>
<td>0 (0-7)</td>
</tr>
<tr>
<td>Receipt of GP referral and consultation at DGH</td>
<td>1 (0-39)</td>
</tr>
<tr>
<td>Consultation at DGH and referral to HPB Unit</td>
<td>18 (3-78)</td>
</tr>
<tr>
<td>Referral to HPB Unit and HPB consultation</td>
<td>13 (2-16)</td>
</tr>
</tbody>
</table>

**Total delay between:**

- **GP referral and definitive treatment at DGH:** 6 (1-71)
- **GP referral and definitive treatment at HPB Unit:** 42 (25-90)

**208 A PROSPECTIVE STUDY OF THE PABA TEST AND FAECAL ELASTASE-1 IN ASSESSMENT OF PANCREATIC FUNCTION**

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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 9 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. Of these patients 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.

**Colorectal posters 209–226**

**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 - 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 (33%) 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**

N.J. Keneflick, C.J. Vaizey, R.J. Nicholls, R. Cohen, M.A. Kamm. St Mark's Hospital, London, UK

**Introduction:** Faecal 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 recruited 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 ano-rectal 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 SF-36 quality of life questionnaire showed an overall improvement. The internal anal sphincter was atrophic in all patients, median width 1.0 mm (0–1.6mm; 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 sclero-derma when other treatments have failed.

**211 PAIN COPING STRATEGIES AND QUALITY OF LIFE IN PATIENTS WITH CHRONIC ANAL FISSURE**

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**Introduction:** To date, there has been little evaluation into the quality of life of patients with chronic anal fissure. This is a prospective study assessing physical and mental health of fissure patients prior to and following topical treatment; pain coping strategies are also identified to see if these affect outcome.
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 (6 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 beneficially affects role physical functioning. Patients’ coping strategies appear to have an influence on outcome, with ignoring sensations being a good predictor of response.

### 212 COLONIC DIVERTICULITIS: A DISEASE ON THE RISE?

S. Subramanian1, A. Tinto2, A. Majeed3, D.M. Melville4, A.R. Hart5, C.R. Mowatt6, J. Nunn7, D.J. Maxwell8, J.Y. Kang9, Departments of ‘Gastroenterology and ‘Surgery, St George’s Hospital, London; ‘Office for National Statistics, London; ‘University College London School of Medicine, University of East Anglia7, Norwich, UK


Materials and Methods: Admission rates for colonic diverticulitis (ICD9: 562.1, ICD10: K57.2–57.9), excluding day cases but including emergency admissions, were obtained from Department of Health Hospital Episode Statistics. Admission rates were available from our database were selected retrospectively for analysis. Paraffin embedded tissue from archival primary tumour material was analysed by immunohistochemical methods for COX-2 and MVD. COX-2 polyclonal human antibody (Cayman) and an endothelial cell antibody, CD-34 (clone QBEND-10, Dako) were used. Staining was performed on deparaffinised sections using the avidin-biotin method. COX-2 was graded by percentage of epithelial cell staining and intensity, MVD was calculated by mean vessel count of five high power fields (x 200) per slide in tumour involved area. Two blinded observers performed both analyses.

Results: Of the 70 cases, 2 were Dukes’ stage A, 26 were stage B, 29 were stage C and 13 were stage D. COX-2 was present in almost 90% of cases. COX-2 staining was present in tumour epithelial cells, inflammatory cells, fibroblasts and endothelial cells. There was variation in staining intensity between tumours. Correlation analysis was performed between intensity of COX-2 expression and MVD. No significant correlation was found between these two groups (r=0.075). No correlation was found between Dukes stage overall or between individual Dukes’ stage and MVD. (Dukes’ B=0.105, Dukes’ C=0.012, Dukes’ D=0.189).

Conclusion: This study demonstrates no association between microvessel density and either the intensity of COX-2 expression in tumour cells or Dukes’ stage. These findings suggest that COX-2 expression does not play a role in determining augmented neovascularisation associated with colorectal cancer. This is in keeping with recent evidence that it is the host COX-2 and COX-1 that are important in angiogenesis.

### 214 CYTOKERATIN IMMUNOREACTIVITY IN BENIGN PERICOLIC LYMPH NODES: AN IMMUNOHISTOCHEMICAL STUDY OF 101 LYMPH NODES

V.I. Shah1, P.J. Arumugam1, J. Beynon1. Singleton Hospital, Swansea, Wales, UK

Background: Several studies have demonstrated scattered single cytokeratin immunoreactive cells in morphologically benign regional draining lymph nodes from cases of Dukes B colorectal cancer. In most studies their presence correlated poorly with tumor recurrence and survival. It is not clear whether these cells represent native cells of the lymph node or occult micrometastasis.

Design: Formalin-fixed paraffin-embedded sections from 101 histologically benign lymph nodes from 38 patients who had undergone colorectal resections for benign conditions (diverticular disease (18), inflammatory bowel disease (11), slow transit constipation (6), valvulosis (1), ischaemia (1), angiodysplasia (1)) and had no history of malignancy at the time of surgery or during a mean follow up period of at least 30 months were immunostained with AE1/AE3 (DAKO, monoclonal,1:100, 30 min, protease 1 pretreatment, 12 min), Cam 5.2 (Becton-Dickinson, monoclonal,1:20, 30 min, protease 1 pretreatment, 8 min) and pan-cytokeratin (DAKO, MNF116, 1:100, 30 min, protease 1 pretreatment, 12 min) on a NEXES autostainer using a Ventana detection system. The morphology of the immunoreactive cells was evaluated and their number scored as 0:absent, 1:1–5%, 2:6–10%, 3+:>10%.

Results: A single cytokeratin positive epithelial cell was identified in 1 (1%) of the lymph nodes in the levels immunostained with AE1/
INTER-EXAMINER REPRODUCIBILITY OF ANORECTAL MOTOR AND SENSORY FUNCTION TESTS

T.J. Nicholls, D. Salanki, T. Mimura, A.V. Emmanuel, M.A. Kamm. Physiology Unit, St Mark’s Hospital, London, UK

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 physiology tests 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 monometry system; anal canal (AS) and rectal mucosa 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, except 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.

HYPERTHERAPY FOR IRITABLE BOWEL SYNDROME: IMPROVEMENT IS LONG-LASTING AND REDUCES HEALTHCARE COSTS

W.M. Gonsalkorale, V. Miller, A. Afzal, P.J. Whorwell. Dept of Medicine, University Hospital South Manchester, M20 2LR, UK

Background: We have shown that hypotherapy (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 (HAD) Scale, (both previously completed pre- and post-HT), iii) a Subjective Assessment Questionnaire (SAQ) assessing effects of hypotherapy, medication use and consultation rates. (P>0.05, N.S.)

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 HT (pre-HT v post-HT; median (IQR): pain severity: 50(37.75) v 25(10,50) v 33(18,50); pain frequency: 50(30,90) v 20(5,50) v 20(1,50); 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: 7(6,8) v 33(22,60) v 39(30,65); forming an overall score: 272(258,287) v 156(91,249) v 171(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.

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, osmotic packs) 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 (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, the 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.

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 anastamosis. 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 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.

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, transudation) is 5% 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.

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 given a median 2 years (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), steatorrhea (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 polypos. Sulfacetamide was always effective in reducing bleeding in those with radiation proctitis. All patients with tenesmus or incontinence improved or were cured with medical therapy including 2 patients with marked anal sphincter changes on endoanal ultrasound. Steatorrhoea was multifactorial, (2, bacterial overgrowth, 2 patients with marked anal sphincter changes on endoanal ultrasound, 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.

TIMING OF OPERATION AFTER RADIOTHERAPY FOR RECTAL CANCER

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Aim: Preoperative adjuvant radiotherapy for rectal cancer has two problems, radiosensitivity 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) (40 Gy, fractionation of 4-8 weeks, n=23), short-course radiotherapy (SC) (25 Gy, 1–2 weeks, n=11), or chemoradiotherapy (CR) (45 Gy, 6–9 weeks, 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, 28.6% and 45% in CRT, 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 pre-therapy biopsies. In SD, the PI in the radiosensitive subgroup was lower than in the radioresistant 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 was steeper in the radiosensitive subgroup, but much steeper than in the radioresistant one and extrapolation back to the end 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 rapidly came and went. Plotting the AI against reduction 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 FAEAL 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 psychosomatic interaction and improved coping strategies appear to be most important, rather than physiological feedback of sphincter function (biofeedback).

222 FAEAL 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 (155 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 smoker, daily bowel frequency, and 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, increasing 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.

**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 and its 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 two of the following: less than 3 defecations per week, straining on more than 25% of occasions, feelings of incomplete evacuation or 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.

**Conclusion:** This study suggests that the prevalence of functional constipation is associated to ageing such as institutionalisation and inactivity. However, no association was found with chronic diseases.

**K-RAS MUTATIONS IN COLORECTAL POLYPS: SITE, HISTOLOGY AND SIZE DO MATTER**

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**Introduction:** Mutation of the oncogene K-ras is thought to be important in the early progression of colorectal carcinogenesis. K-ras is involved in the cell signalling pathway and it 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.

**Methods:** Polyps were collected during colonoscopy from 55 successive patients and control tissue obtained from 20 other patients. DNA was extracted from the fresh tissue and mutations were detected following PCR and restriction enzyme (mva1) digestion. Ethical approval was obtained.

**Results:** Mutations of K-ras were found in 21% of the 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 K-ras. 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 more tubulovillous/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.

**DO CYTOKINE LEVELS PREDICT PROGNOSIS IN COLORECTAL CANCER?**

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**Aims:** To assess levels of faecal calprotectin and the factors that could effect them in a healthy late middle aged population and to understand the role of this important oncogene in adenoma growth and progression to carcinoma.

**Methods:** Heparinised venous blood samples were taken from fifty-three patients (34M &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 F=0.05) Similarly, those with high postoperative IFN γ levels developed local recurrence later than those with lower levels. (Correlation coeff= 1αt F=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 F=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 F=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 immunosuppressive 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 immunosuppressive cytokines need close surveillance for the development of loco-regional or systemic relapse.

**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
Gastrointestinal posters

227 MANAGEMENT OF PEPTIC ULCER DISEASE IN PRIMARY CARE
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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 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 in the preceding year [Total GP population 176,268] 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 and 8.7% both). H. pylori prevalence was 65.6% in patients who 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%). 270 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 ESOMEPR AZOLE 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 volunteers.

Methods: 27 H. pylori-negative subjects underwent two 24-hour test periods, 14 days apart, whilst taking a placebo. An additional 6 subjects underwent a 24-hour test period over 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>0–24</sub>) were calculated, and compared using ANOVA.

Results: There were no statistically significant differences in mean AUC<sub>0–24</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 pH >4 was significantly higher on RAB 20 mg than ESO 40 mg (pH >3: 42.1%, SD=23.5 and 22.1%; 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 pH >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: 65.4%, 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 Eisai 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.

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EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON ENDOTHELIAL CELL PROLIFERATION AND MIGRATION IN VITRO

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Background/Aims: Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with delayed healing of peptic ulcers which in turn is likely to be found in the stomach after an oral dose) on PGE2 production compared with control incubations. Higher dilutions of AV inhibited the migration of gastric cell lines. Results were corrected for cell numbers estimated by MTT assay. Western blotting was used to detect COX2 expression 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 gastric epithelial cells in culture.

Results: The stimulatory effect of aloe vera gel (in a concentration likely to be 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.

Conclusion: The stimulatory effect of aloe vera gel (in a concentration likely to be 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 232

<table>
<thead>
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<th>AV dilution</th>
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<th>1 in 100</th>
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<td>(0.518)</td>
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<td>MKN45</td>
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<td>(319-1064)</td>
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Expression of COX 2 was upregulated by incubation in 1:10 AV in MKN7. In MKN 45 cells COX2 was activated by 1:10 AV.

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 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

<table>
<thead>
<tr>
<th>Prevalence/ 1000 persons</th>
<th>1994</th>
<th>1998</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Age standardised prevalence</td>
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<tr>
<td>Prevalence &lt; 65 years</td>
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<tr>
<td>Prevalence &gt; 65 years</td>
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</tr>
<tr>
<td>% prescribed PPI</td>
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</tr>
<tr>
<td>% prescribed H2 antagonist</td>
<td>72.3</td>
<td>70.8</td>
</tr>
</tbody>
</table>


S. Subramanian1, A. Tinto1, J. Higham2, A. Majeed1, J.Y. Kang1. 1Dept of Gastroenterology, St George’s Hospital; 2Office for National Statistics; 1University College, London, UK

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,
A PROSPECTIVE STUDY OF GASTROENTEROLOGY CONSULTATIONS IN AN URBAN TEACHING HOSPITAL

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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 specialties. Average delay before consultation was less than one working day. The referral sources were predominantly from respiratory medicine, general surgery, nephrology and neurosciences. The commonest reasons for referral were abdominal pain (15.8%), PEG tube insertion (13.6%), diarrhoea (12.8%), and abnormal liver blood tests (10%). Ongoing care and subsequent problems were dealt with satisfactorily in a consultation setting, with only a minority requiring transfer to a Gastroenterology team during in-patient stay but a significant percentage required endoscopic procedures and follow up at GI clinic after discharge. Various disciplines (drug-induced hepatitis, diarrhoea, colitis, peptic ulceration, pancreatitis etc) accounted for 6.2% of consultations. Among referral for PEG tube insertion, over a quarter were considered better managed without a PEG.

The provision of the GI inpatient consultation services constitutes a significant and increasing proportion of the workload in Gastroenterology. Referral problems assessed were dealt with satisfactorily in a consultation setting, with only a minority requiring transfer to a Gastroenterology team during in-patient stay but a significant percentage required endoscopic procedures and follow up at GI clinic after discharge. Consultations for PEG tube insertion were especially worthwhile.

GASTRODUODENAL MUCOSAL DAMAGE IN MAJOR BURNS: HOW SIGNIFICANT IS IT?

University Departments of Surgery and Pathology, North Colombo General Hospital Ragama, Sri Lanka

Introduction: Acute gastroduodenal 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 injuries. Patients and Methods: 18 patients (13 females, median age 23 years) were included in the study (burn surface area >20%). In patients completing the trial protocol.

Results: 2(11.1%) patients had mild upper abdominal pain. 2(11.1%) patients had abnormal UGIE findings 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=66) 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 rate 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. Only one of the patients had persistent H. pylori infection (NS).

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 effective and equally efficacious for maintenance of gastroduodenal mucosal integrity during continued NSAID use. WARFARIN ANTI-COAGULATION CONTROL IN PATIENTS TAKING PROTON PUMP INHIBITORS

C.F. Donnellan, S. Dass, F. Dunn, M.A. Hull. Dept of Gastroenterology, St James’s University Hospital; The Anti-coagulation Clinic, Seacroft Hospital, Leeds, UK

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 anticoagulation (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%]) and 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 PPI 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<0.0001) 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).
Conclusion: PPI therapy was associated with a small, but significant decrease in AC control although the increased age and lower testing frequency in the PPI patient group may have contributed to this. A prospective study, including data on other drug use eg anti-epileptics as well as on clinically significant bleeding episodes, is warranted.

**238 ERADICATION OF HELICOBACTER PYLORI: CLINICAL PRACTICE AMONG HOSPITAL CONSULTANTS IN THE UNITED KINGDOM**

S. Arroor, S.G. Jacob

**Aim:** To assess the clinical practice of hospital doctors across United Kingdom in eradication of Helicobacter pylori.

**Methods:** The study was carried between October 2000 and May 2001 during which time a questionnaire was sent to 130 gastroenterologists and 130 general and upper GI surgeons across United Kingdom inquiring the following: (1) The pathological conditions in which they chose to eradicate the organism - Gastric oesophageal 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:** 61.3% gastroenterologists and sixty-two (47.5%) patients 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.

**239 A 5-YEAR, DOUBLE-BLIND, RANDOMISED COMPARISON OF RABEPRAZOLE AND OMEPRAZOLE IN GORD MAINTENANCE TREATMENT: GASTRIC BIOPEPSY RESULTS**

B. Thjoddeifsson1, N.M. Miller1, K.D. Bardhan2. 1University Hospital, Reykjavik, Iceland; 2Eisai Ltd, London, UK; 3Rotherham General Hospital, Rotherham, UK

**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 in the antrum, but only in the 10 mg rabeprazole group in the corpus. Inflammation, activity of inflammation and mucosal atrophy were all more severe in *H. pylori* positive patients than in *H. pylori* negative patients. Those variables generally improved during the study, except inflammation in the corpus, which improved only in the 10 mg rabeprazole group and clinical 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.

**240 THE INFLUENCE OF SMOKING AND NSAIDS ON SYMPTOM SEVERITY IN PATIENTS TAKING ANTI-SECRETORY THERAPY**

A.J. Morris, C. Craig, C. Moran, K. Harden, H. Burns, A. Power, D. Walsh, R.C. Stuart. ACID 1 study group, Digestive Disease Directorate, Glasgow Royal Infirmary, Glasgow, UK

**Aim:** In a large general practice study (ACID1) of *H. pylori* eradication in patients receiving maintenance anti-secretory therapy we investigated the effects of smoking and NSAID use on dyspepsia severity scores.

**Patients/Methods:** 4003 patients receiving maintenance therapy (≥3 scripts/year of a H2RA or PPI drug) were invited to a nurse led community dyspepsia clinics. 2353 attended and completed a modified Glasgow Dyspepsia Severity Score (GDSS) and Digestive Disease Quality of Life Score (DDQ). Prescribing data was collected for the 12 months prior to study enrolment from computer and case note records.

**Results:** Mean scores are presented in the table. Aspirin use alone was associated with lower GDSS but, in combination with other NSAIDs, it resulted in higher symptom severity and lower quality of life scores. There was no correlation between smoking and GDSS or DDQ scores. See table.

<table>
<thead>
<tr>
<th>Patients/NSAID use</th>
<th>Mean GDSS</th>
<th>Mean DDQ</th>
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<tbody>
<tr>
<td>NSAID use</td>
<td>5.36*</td>
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</tr>
<tr>
<td>No NSAIDs</td>
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<tr>
<td>Other NSAID</td>
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<tr>
<td>Aspirin/Other NSAID</td>
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<td>Ex smoker</td>
<td>5.59</td>
<td>2.61</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5.89</td>
<td>2.59</td>
</tr>
</tbody>
</table>

p<0.001 ANOVA.

**Conclusions:** In dyspeptic patients receiving acid suppressing agents: (1) Aspirin use, on its own, was associated with lower symptom severity scores but, when combined with other NSAIDs, it resulted in higher symptom severity and poorer quality of life scores. (2) Smoking did not affect symptom severity or quality of life scores in patients.

**241 NSAID PRESCRIBING GUIDELINES: CONTINUED ULCER BLEEDING DESPITE MANAGEMENT CONSENSUS**

M.M. Skelly1, B. Pick1, R.F.A. Logan1, C.J. Hawkey1. Division of ‘Gastroenterology’ & ‘Dept of Public Health and Epidemiology, University Hospital, Nottingham, UK

**Introduction:** Use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with peptic ulcer disease (PU) complications. Local consensus guidelines on NSAID prescribing include a preference for use of ibuprofen ≤ 1200mg if NSAID use was unavoidable, avoidance of slow release preparations, use of a COX II inhibitor or co-prescription of a proton pump inhibitor or misoprostol for patients at high risk of ulcer complications (PU history, age ≥ 65, use of NSAID other than ibuprofen, high NSAID doses, concomitant corticosteroids or anti-coagulation.

**Aim:** To study all patients admitted with upper gastrointestinal haemorrhage (UGH) and to determine if prescribing guidelines were being followed in those cases on NSAIDs.

**Method:** All patients admitted with UGH over 4 months were identified prospectively. Details were collected regarding demographics, aspirin or NSAID use, co-morbidity and features of the bleeding episode. Patients found to have bled from varices were excluded from analysis.

**Results:** Ninety four patients were admitted with confirmed non-variceal upper gastrointestinal haemorrhage (53 men; mean age...
IDENTIFICATION OF POSSIBLE GUT HOMING STREPTOCOCCUS FAECIUM, A POSSIBLE PROBIOTIC ASCA AND ANCA IN THE DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE AND OTHER DIARRHOEAL ILLNESSES

M. Harbord1, R. Day2, A. Hankin1, S. Bloom1, A. Forbes1, A.W. Segal1.
1Department of Medicine, University College, London; 2St Mark’s Hospital, London, UK

Background: Neutrophil migration into the tissues is defective in CD during G-CSF administration. The data indicate that a cell wall component of S. faecium, a gut commensal and putative probiotic, down-regulates TNFα 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 cytokines.

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 (Nissle strain) at the equivalent of 10^9 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 EUSA.

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-10 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 TNFα 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 wall components.
result expected in Crohn’s and ANCA+ASCA- in UC. We have tested patients with diarrhoeal disease.

**Background:**

Crohn’s disease is an inflammatory bowel disease characterized by chronic inflammation of the gastrointestinal tract. The precise cause of Crohn’s disease is unclear, but it is believed to be a combination of genetic, environmental, and immunological factors. Recent studies suggest a role for defects in the immune system, specifically in the regulation of inflammatory responses.

**Methods:**

Biopsies were taken from patients with Crohn’s disease and analyzed for ASCA and ANCA expression. The samples were obtained from patients who were being treated for Crohn’s disease at a tertiary care center.

**Results:**

ASCAs were found in 32% of the Crohn’s disease patients, and ANCAS were found in 28% of the same patients. The results suggest that ASCA and ANCA may play a role in the pathogenesis of Crohn’s disease.

**Conclusions:**

The presence of ASCA and ANCA in patients with Crohn’s disease suggests a potential role for these autoantibodies in the disease process. Further studies are needed to confirm these findings and to understand the role of ASCA and ANCA in the pathogenesis of Crohn’s disease.
**Aim:** We investigated the hypothesis that Helicobacter pylori (HP) infection is associated with a decreased prevalence of atopy (asthma, allergic rhinitis and eczema).

**Methods:** 26,203 individuals aged 20–59 years from 7 primary care centres in the SW of England were invited to participate in a randomised controlled trial of HP eradication. 10,537 agreed to participate and underwent a 13C urea breath test. 3,244 individuals (2,165 HP−ve, 1,079 HP+ve) supplied medication details on a validated questionnaire. Inhaled/oral bronchodilators, inhaled corticosteroids or Cromoglicate therapy were used as surrogate markers for asthma. Similarly oral antihistamines and topical corticosteroids were used as markers for allergic rhinitis and eczema respectively.

**Results:** Those individuals found to be HP positive were less likely to be taking a medication for asthma, eczema or allergic rhinitis (OR 0.57; 95% CI 0.48–0.69). hpBD-2 mRNA expression was quantified by RT-PCR.

**Conclusions:** Those individuals found to be HP positive were less likely to be taking a medication for asthma, eczema or allergic rhinitis (OR 0.57; 95% CI 0.48–0.69). hpBD-2 mRNA expression was quantified by RT-PCR.}

**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, in particular in models of colitis, we studied the effect of probiotic bacteria on NK cell activation and cytokine production.

**Methods:** Whole blood and monoclonal cells from colonic biopsies were cultured overnight with Lactobacillus acidophilus, Streptococcus faecalis and Escherichia coli (Nissle strain). Expression of the activation antigen CD69 and intracellular cytokines (IFN-γ, IL-10 and IL-4) were assessed by flow cytometry.

**Results:** At high concentrations (10⁸ colony forming units per millilitre), cell wall fractions of all three probiotic bacteria induced expression of CD69 and IL-4 (greater than 97% of blood NK (CD3−CD8+) cells). The dose required for 50% maximal CD69 expression differed between the bacteria: Escherichia coli–Lactobacillus acidophilus–Streptococcus faecium. CD69 expression was induced to a lesser extent on CD8+ (35%) and CD4+ (20%) T cells. The soluble fraction of Escherichia coli–Nissle strain) but not Streptococcus faecium also activated NK cells. IFN-γ, IL-10 and IL-4 production by NK cells was detected on exposure to the different bacteria, demonstrating the functional significance of this NK activation. In colonic tissue, there was also a baseline expression of IFN-γ by NK cells, indicating that these cells are activated in vivo, possibly as a result of local exposure to commensal bacterial antigens. This activation was further increased by all of the probiotic bacteria.

**Conclusions:** Probiotic bacteria modulate innate immunity by activating and stimulating cytokine production by NK cells. The effect varied with different bacterial dose, fraction and probiotic species. Modulation of innate immunity, including NK cells, may contribute to the therapeutic action of probiotic bacteria in intestinal inflammation.

**Introduction:** Interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α) are pro-inflammatory cytokines that play a key role in the regulation of immune responses, including immune cell activation and cytokine expression. IFN-γ is also an important anti-microbial agent, and plays a role in the control of viral infections.

**Methods:** CD8+ T cells were isolated from peripheral blood lymphocytes of healthy individuals using magnetic bead technology. Cells were cultured in the presence of various concentrations of IFN-γ and TNF-α, and the expression of the inflammatory cytokines IL-6 and IL-1β was measured by ELISA.

**Results:** IFN-γ and TNF-α significantly increased the expression of IL-6 and IL-1β in CD8+ T cells. The effect was dose-dependent, with the highest concentrations of cytokines resulting in the greatest increase in cytokine expression.

**Conclusions:** IFN-γ and TNF-α are potent stimulators of cytokine expression in CD8+ T cells, and may play a role in the activation of these cells during immune responses.

**Administration of probiotics to patients with Helicobacter pylori (HP) infection:**

**Aim:** To evaluate the effects of probiotics on the immune response to HP infection.

**Methods:** A randomised controlled trial was conducted in patients with HP infection. The study group received probiotics, while the control group received a placebo. The immune response to HP infection was assessed by measuring the levels of IFN-γ and TNF-α in the blood.

**Results:** The study group showed a significant increase in IFN-γ and TNF-α levels compared to the control group, indicating a positive effect of probiotics on the immune response to HP infection.

**Conclusions:** Administration of probiotics to patients with HP infection may enhance the immune response to HP infection, and further studies are needed to determine the optimal probiotic regimen and duration of treatment.

**DYSPEPSIA IS MORE COMMON IN ELDERLY WOMEN**

**Background:** Dyspepsia is a common symptom in the general population. This has not previously been formally studied in the older population, despite them having a higher prevalence of Helicobacter pylori (HP) infection.

**Aims:** To conduct a questionnaire survey of the general population of older adults in 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. This ascertained basic demographic details and asked whether subjects suffered from waterbrash, vomiting, bloating, nausea, upper abdominal pain or heartburn on more than one occasion or for more than one day in the previous month. Participants were asked how often they took any medication for these symptoms and requested to send a sample of saliva collected in a cotton salivette (Sarsted) by return of post. The saliva samples were analysed for antibodies to HP in order to determine seropositivity as previously described (Guarner 2000; [suppl II], A67: W141). Analyses were made using Chi squared / Fisher’s Exact test, or Mann Whitney U test.

**Results:** In total 1116 subjects (60%) returned both the questionnaire and a usable sample. Of these 616 (55%) were eligible as women. 284 (25%) were determined as seropositive to HP infection. 516 (46%) 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 it is more common in women. It is not related to NSAID use, smoking or HP infection, and deserves further investigation.

**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**

**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 transmural intestinal segments separately.

**Methods:** A model of distant aboral secretion was created in anaesthetised 200g male Whistar rats. CT (50 µg/ml), LT (50 µg/ml), STa (20 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 (Inderal); 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.
**Abstract 255**

<table>
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<th>1</th>
<th>10</th>
<th>100</th>
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<tbody>
<tr>
<td>TGF-β (pg/ml)</td>
<td>514</td>
<td>*720</td>
<td>*830</td>
<td>*1316</td>
<td>*1122</td>
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<td>IL-8 (pg/ml)</td>
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<td>245</td>
<td>256</td>
<td>249</td>
<td>336</td>
<td>*426</td>
<td>*503</td>
</tr>
</tbody>
</table>

*p<0.03.

**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 through intrinsic or extrinsic neurones. 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.

**PATHOGENIC BACTERIA STIMULATE COLONIC DENDRITIC CELLS TO PRODUCE PRO-INFLAMMATORY IL-12 WHILE THE RESPONSE TO PROBIOTIC BACTERIA IS TO PRODUCE ANTI-INFLAMMATORY IL-10**


**Introduction:** Intestinal dendritic cells (DC) sample luminal contents and play a central role in the regulated response to the commensal gut flora. This is mediated in part by cytokine production following exposure to bacterial products, and results in a balance between pro- and anti-inflammatory responses. Cytokine production by murine colonic DC was assessed after stimulation by a component of pathogenic bacteria.

**Methods:** DC were identified as CD11c+MHC class II+ cells in mononuclear cell preparations obtained by collagenase digestion of colonic tissue. Production of IL-12, IL-10 and IL-4 in response to LPS from C. difficile following infection with toxin-secreting S.S. Johal, K. Solomon, J. Webb, S. Dodson, Y.R. Mahida. Division of Gastroenterology, University Hospital, Nottingham, UK

**Intestinal dendritic cells (DC) sample luminal contents and play a central role in the regulated response to the commensal gut flora. This is mediated in part by cytokine production following exposure to bacterial products, and results in a balance between pro- and anti-inflammatory responses. Cytokine production by murine colonic DC was assessed after stimulation by a component of pathogenic bacteria and a putative probiotic bacterium.**

**Results:** CD11c+MHC class II+ cells were isolated from RPMI cultures of colonic cells, and their proportion of IL-12 producing DC by 4–10 fold. In contrast, IL-10 was increased by 50% indicating cross-regulation of the cytokine production.

**Conclusions:** There was a dramatic and highly significant inhibition of IL-12 production following infection with 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 chemotaxin IL-8 and rapid, irreversible loss of barrier function. Thus the level of exposure of intestinal epithelial cells to C. difficile toxins may determine the development and severity of colitis.

**NITRIC OXIDE (NO) RELEASED BY GLYCO-SNAP-1 SIGNIFICANTLY INHIBITS THE LPS STIMULATED PRODUCTION OF IL-1β BUT NOT TNF-α BY HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCs)**

J. Burdass, J. Smith, C.J. Hawkey. University of Nottingham, Division of Gastroenterology, UK

**Introduction:** NO donating anti-inflammatory drugs such as NO-NSAIDs and Nitroprednisolone are currently being evaluated for enhanced anti-inflammatory properties believed to be related to NO release. PBMC’s are recruited to 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 1mM 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 TNF-α release in a concentration related response (R²=0.8799). NO released from G-SNAP-1 is a potent inhibitor of the pro-inflammatory mediator IL-1β production by human PBMC’s but not TNFα.

**Inhibition of IL-1β release by G-SNAP-1**

**Changes in epithelial barrier and cytokine release in response to C. difficile toxin A**

S.S. Johal, K. Solomon, J. Webb, S. Dodson, Y.R. Mahida. Division of Gastroenterology, University Hospital, Nottingham, UK

Following infection with toxin-secreting C. difficile, presentation can range from severe colitis to no colonic inflammation. We investigated changes in epithelial barrier and release of transforming growth factor-β (TGF-β) and interleukin-8 (IL-8) in response to C. difficile toxin A.

**Conclusion:** NO released from G-SNAP-1 is a potent inhibitor of the pro-inflammatory mediator IL-1β production by human PBMC’s but not TNFα.
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 cause, timeline, consequences and 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 was 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.

**Conclusions:** This pilot study has shown that the initial health perception of IBS patients remains stable during the first couple 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.

**CIGARETTE SMOKING AND CROHN’S DISEASE: EFFECT ON DISEASE LOCALISATION**

D.P. Hurlstone, M.J. Carter, D.S. Sanders, S. Mitchell, Z. Harclerode, A.J. Lobo. Gastroenterology and Liver Unit, Sheffield Teaching Hospitals, UK

**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 2x2 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=2.43, 95%CI: 1.66–3.43). Significance remains, comparing isolated colonic with ileo-caecal/SBD (p=0.0001, OR=3.71, 95%CI: 1.77–4.14).

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Smokers</th>
<th>Ex-smokers</th>
<th>Non-smokers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileo-caecal/SBD</td>
<td>95</td>
<td>26</td>
<td>82</td>
<td>203</td>
</tr>
<tr>
<td>Mixed</td>
<td>40</td>
<td>15</td>
<td>50</td>
<td>105</td>
</tr>
<tr>
<td>Colonic</td>
<td>49</td>
<td>59</td>
<td>95</td>
<td>203</td>
</tr>
</tbody>
</table>

**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.

**OUTCOME OF ENTERAL FEEDING FOR NEWLY DIAGNOSED CROHN’S DISEASE**

E. Ali, F. Crouchman, N. Meadways, I.R. Sanderson, N.M. Croft. Dept of Adult and Paediatric Gastroenterology, Barts and the London, Queen Mary’s School of Medicine and Dentistry, London, UK

**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. In...
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 (Modulen, Nestle UK) was started in 30/31 patients, one refused and was treated with steroids. 24/30 (80%) went into 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 thioprine. 2/7 children who required steroids at presentation remain in remission, 5/7 have 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 the relapses. During the majority (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.

261 LOW DOSE ORAL METHOTREXATE FOR THE MEDICAL TREATMENT OF STEROID DEPENDANT/RESISTANT CROHN'S DISEASE. EXPERIENCE IN A SINGLE LARGE IBD CLINIC

A. Ansari, M. Yaneza, J. Hurst, J. Sanders. Guy's and St Thomas' Hospital, London, UK

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 CD despite AZA (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 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 thioprine. 2/7 children who required steroids at presentation remain in remission, 5/7 have 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 the relapses. During the majority (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.

262 COMBINATION IMMUNOMODULATORY THERAPY WITH CYCLOSPORIN, AZATHIOPRINE AND CORTICOSTEROIDS IN SEVERE ULCERATIVE COLITIS: THE EDINBURGH EXPERIENCE OF OUTCOME

S. Campbell, S. Ghosh. The Gastrointestinal Unit, University of Edinburgh, Department of Medical Sciences, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK

Background: Cyclosporin is a fungal metabolite and is a powerful immuno-suppressant. While response to intravenous steroids is in excess of 60%, the remainder of patients are left with the options of curative proctocolectomy or administration of intravenous rescue therapy with cyclosporin. There have been conflicting reports with regard to efficacy of IV cyclosporin in acute UC, and there are serious concerns about potential toxicity and opportunistic infections such as pneumocystis carinii pneumonia. To date there has been a paucity of data available to help guide the gastroenterologist in the use of cyclosporin.

Methods: Between 1994 and 2001, there were 16 patients who had received intravenous cyclosporin for acute exacerbation of their known UC (7 female, 9 male, mean age 33 years). All patients were treated with and were refractory to IV methylprednisolone (60mg/24hrs). Patients were discharged on a regimen of oral cyclosporin, oral steroids and oral azathioprine.

Results: Median disease duration was 5.4 years (range 0.9–25 years). All patients were initially treated with cyclosporin at a dose of 4mg/kg/day. Nine patients were simultaneously started on oral azathioprine (median dose 1.8mg/kg). Seven patients underwent surgery (proctocolectomy), although none had surgery after 6 months. Comparisons were made between patients who had <7 days IV steroid versus >7 days IV steroid, and other subgroups such as stool frequency at 3 days and CRP at 3 days. There was no statistical significant differences between these groups.

Conclusion: Initial response rate was high (69%). Side effects were documented in the majority of patients, but none of the patients had to discontinue treatment because of these. At 3 years follow-up, 56% of patients avoided surgery. Median bowel frequency at day 3 was higher in patients who finally underwent surgery. Cyclosporin has a useful role as a 3rd line drug therapy for acute UC patients.

263 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 colonoscopy reports were retrospectively reviewed with respect to age, sex, indication for the exam 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 with known UC (7 female, 9 male, mean age 33 years). All patients were treated with and were refractory to IV methylprednisolone (60mg/24hrs). Patients were discharged on a regimen of oral cyclosporin, oral steroids and oral azathioprine.

Conclusion: It has been shown previously that sodium picosulphate can cause colonic ulceration. Our series confirms this finding which might potentially lead to an incorrect diagnosis and unnecessary treatment. The use of sodium phosphate preparation in patients suspected of having inflammatory bowel disease may be inadvisable.

264 ROLE OF THE 5Q31 CYTOKINE CLUSTER (IBDS LOCUS) IN GENETIC SUSCEPTIBILITY TO ULCERATIVE COLITIS AND CROHNS DISEASE IN THE UK


Introduction: Genetic studies in inflammatory bowel disease have identified several susceptibility loci. Recently genetic variation in the 5q31 cytokine cluster has been linked to and strongly associated with Crohn's disease in the Canadian population (IBDS locus, Rioux et al.,
Abstract 265

CD14 AND PPARγ POLYMORPHISMS: CANDIDATE GENES FOR IBD?

D.P.B. McGovern, K. Negoro, D.A. van Heel, N. Lench, D.P. Jewell. Wellcome Trust Centre for Human Genetics and Gastroenterology Unit, University of Oxford, UK

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 3p25, a CD locus (ILOC score 4.9) (Duer et al, AGA 2001). PPARγ agonists antagonize monocyte function through inhibition of activated protein 1 and NFκB. Trogilitazine (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: See table.

Abstract 266

Table 1 Allelic frequencies of 1007fs in study population (comparisons are between CD and HC using chi squared)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CD14</th>
<th>Pro12Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>249</td>
<td>9/25</td>
</tr>
<tr>
<td>UC</td>
<td>113</td>
<td>9/25</td>
</tr>
<tr>
<td>CD (overall)</td>
<td>131</td>
<td>9/25</td>
</tr>
<tr>
<td>CD (NOD2+)</td>
<td>131</td>
<td>9/25</td>
</tr>
<tr>
<td>CD (NOD2)</td>
<td>98</td>
<td>9/25</td>
</tr>
</tbody>
</table>

Key: TR - Transmitted, NT - Non transmitted
NOD2+ - CD phenotype containing at least 1 of the NOD2 mutations associated with CD

Conclusions: The CD14 promoter and Pro12Ala polymorphisms are not statistically associated with susceptibility to IBD. However Pro12Ala requires further investigation in a larger cohort of NOD2 positive CD.

Abstract 266, Table 2 Allelic frequency of 1007fs in published series and present study (8 out of the 9 patients heterozygous for 1007fs had ileal disease)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study λ</th>
<th>Edinburgh λ</th>
<th>x²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hampe et al</td>
<td>97/608</td>
<td>9/180</td>
<td>14.014</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hugot et al</td>
<td>112/936</td>
<td>9/180</td>
<td>7.587</td>
<td>0.006</td>
</tr>
</tbody>
</table>

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ARE PRIMARY SCLerosing CHolangitis (PSC) ASSOCIATED COLITIS AND UlCERATIVE COLITIS IDENTICAL? EVIDENCE FROM EXTRANTESTINAL MANIFESTATIONS (EIMS)


Background: The association between PSC and ulcerative colitis is well documented, with up to 80% of PSC patients having evidence of colonic inflammation. Most patients with PSC have a pancolitis which tends to run a quiescent course. However it is associated with a particularly high risk of colonic malignancy, and it has been suggested that PSC associated colitis is a different clinical entity from typical UC. We have previously reported a series of patients with severe PSC and seropositive rheumatoid arthritis. This study was undertaken to compare the prevalence of EIM’s in PSC colitis and UC.

Aims: To compare the frequency of EIM’s in PSC colitis and UC.

Methods: The notes of 976 patients with UC and 72 patients with PSC colitis were reviewed, and information on general disease characteristics and EIM’s was obtained. This information was validated by a patient questionnaire administered in outpatients. The prevalence of published data. Explanations for this discrepancy may include phenotypic heterogeneity in age of onset, extent of involvement and familial tendency and ethnicity.


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IBD associated arthritis, rheumatoid arthritis, erythema nodosum and uveitis was 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.

<table>
<thead>
<tr>
<th>EIM</th>
<th>PSC Colitis N=72</th>
<th>UC N=976</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>Peripheral 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.

**A NEW ORAL INHIBITOR OF TUMOUR NECROSIS FACTOR EFFECTIVELY TREATS PRIMATE MODELS OF COLITIS**

S. Ganesan1, S. Iyer2, S.P.L. Travis3, J. Vogt2, R. Jazrawi1, R.J. Tesi1, R. Beulow.
1Phase 1 Clinical Trials Unit, Plymouth; 2Sangstat Medical Corporation, Fremant, CA; 3Gastroenterology Unit, Oxford, UK

**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 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 (0-normal; 1- loose; 3-liquid; 4-bloody) 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. Duration of response after treatment was recorded.

**Conclusions:** Oral RDP-58 is safe and rapidly effective in primate colitis, with a prolonged duration of effect after dosing for 3 weeks. Phase 1 human volunteer studies are indicated.

**CIRCULATING MUCOSAL HOMING (β7+) MEMORY T CELLS ARE DECREASED IN NUMBER AND DISPLAY ALTERED CYTOKINE PRODUCTION IN CROHN'S DISEASE**

A.L. Har1, 2, R. Rigby1, A. Jones1, M.A. Kam1, S.C. Knight1, A.J. Stagg2.
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 back to the gut. Monoclonal antibodies to α4(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–leucocytes from 7 Crohn’s disease patients (CDAb>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 (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 monocyte 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.

**CYTOCHROME P450 AND MULTIDRUG-RESISTANCE GENE POLYMORPHISMS: PREDICTORS OF THE NEED FOR COLECTOMY IN ULCERATIVE COLITIS?**


**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 CYP3A5. SNPs in CYP3A5*3 cause alternative splicing and protein truncation resulting in the absence of CYP3A5 in tissues. The number of T cells was the same in both groups but a greater proportion were memory T cells in Crohn’s disease.

**Methods:** Patients with IBD poorly responsive to medical therapy have increased MDR-1 expression. Recently, homogoligy for a polymorphism in exon 26 of MDR-1 has been associated with lower duodenal MDR-1 expression and elevated serum substrate (digoxin) levels. 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.

**Results:** CYP3A5*3: Allele frequency was not significantly different between the two groups: colectomy 8.5%, non-colectomy 5.6% (p = 0.33).

**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.
MECHANISMS OF IMPAIRED GROWTH IN PAEDIATRIC CROHN’S DISEASE: DIRECT EFFECTS OF TNF-α ON GROWTH PLATE CHONDROCYTES

A.B. Ballinger, V. McDonald. Adult & Paediatric Gastroenterology, Barts & The London, Queen Mary’s School of Medicine & Dentistry, London, UK

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.

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 then sent out which required 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.

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-oxidant 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 oxidant 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 or fall in albumin or AOC. 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 x 10^3 to 360 ± 75), CRP (11 mg/l ± 13 to 13 ± 13), albumin (41 g/l ± 4 to 41 ± 5), Harvey-Bradshaw Index (for CD patients) (3 ± 2.4 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 baseline) (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.

Abstract 272

<table>
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<tr>
<th>Age standardised admission rates per 100,000</th>
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<tbody>
<tr>
<td>1989/90</td>
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<tr>
<td>M</td>
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<tr>
<td>Crohn’s disease</td>
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<tr>
<td>% with operation</td>
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<td>Ulcerative colitis</td>
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findings could be due to changes in management practice they may reflect true trends in the epidemiology of these two diseases.
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/8x10^9 (median 172) red cells and the azathioprine dosages from 0.3 to 2.8 mg/kg (median 1.6) in the n=89 cohort. Within this group there was no difference in TGN range or azathioprine dosages for patients on monotherapy (n=20), azathioprine and steroids (n=15) or azathioprine and 5-amino salicylic 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 concomitant steroid or aminosalicylate therapy. In addition, these metabolites can be used as indicators of compliance with oral azathioprine therapy. 10% of patients were non-compliant.

INFLIXIMAB FOR CROHN’S DISEASE: ONE UNIT’S EXPERIENCE

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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. Fostulating CD rarely heals with conventional medical therapy. Clinical indications for infliximab can be used as indicators of compliance with oral azathioprine therapy. 10% of patients were non-compliant.

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 maximal medical therapy. Clinical indications for infliximab therapy were fistulizing CD (n=5) and refractory luminal CD (n=14). 11/19 had undergone previous GI surgery. 18/19 were unresponsive to and 1 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 antihistamine 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 fistulating CD, closed their fistulae. Patients requiring surgery (n=4) following therapy had all undergone surgery for their CD previously. No side effects were reported on 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 or fistulizing CD.

DRB1*15 MOLECULAR SUBTYPING CONFIRMS THAT CAUCASIAN 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*1515 molecular subtyping has been carried out in 5 previous studies of Caucasian patients. Only one (Traftenberg et al Hum. Immunol. 2000; 61:326) reported an association with DRB1*1502.

Aims: To determine whether DRB1*15 molecular subtypes or linked polymorphisms in nearby genes confer susceptibility to caucasia UC in a large cohort of accurately phenotyped patients.

Methods: LD mapping of 340 polymorphisms across 24 genes was 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: DBB1*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 *A3201-Cw4*11202-*B8*2501-MICA*00901-MICB*0102-DRB5*0101-DRB1*1502-DQB1*0601 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.

TUMOUR NECROSIS FACTOR ALPHA (TNFα) PROMOTER POLYMORPHISMS AND COLITIS ASSOCIATED COLORECTAL NEOPLASIA (CANCER)

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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 -308CA. TNFα -308A allele frequency was increased in CACRN (38.3%) vs control (21.2%; 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 -308A 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 inactive Crohn’s disease (CD). This effect may result from an impaired micro-vascular 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 micro-vascular 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 CD blister at 24 h was lower than in the control group (mean ± SEM: CD 4.23±10² ± 1.664 cells/ml; controls 5.68±10² ± 1.630 cells/ml). Micro-vascular 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).

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<th>Organ wt</th>
<th>T/control</th>
<th>Control/colitic</th>
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<tr>
<td>SV (mg)</td>
<td>156 ± 28</td>
<td>104 ± 28&lt;sup&gt;1&lt;/sup&gt;</td>
<td>157 ± 26</td>
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<tr>
<td>Prostate (mg)</td>
<td>128 ± 19</td>
<td>70 ± 17&lt;sup&gt;1&lt;/sup&gt;</td>
<td>104 ± 19&lt;sup&gt;1&lt;/sup&gt;</td>
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<sup>1</sup>P<0.01 vs HC; <sup>2</sup>P<0.02 vs T/colitic; <sup>3</sup>P=0.04 vs HC.

Conclusion: Inhibitory effects of intestinal inflammation on end-organ responsiveness are overcome with testosterone, suggesting that any resistance is at least only partial. Testosterone treatment may be useful to induce puberty in young patients with Crohn’s disease and delayed puberty.

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 gamma (PI(3)Kγ) leads to altered cell activation, growth and apoptosis. Mice deficient in PI(3)Kγ develop invasive adenocarcinoma of the colon, while mice lacking Gis2, a signalling protein upstream of PI(3)K, develop ulcerative colitis and adenocarcinoma. The PTEN tumour suppressor gene opposes the action of PI(3)Kγ and mice deficient in PTEN develop tumours and autoimmune phenomena. We therefore hypothesised that abnormal PI(3)Kγ 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 dysplastic 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, endoscopic 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/adenomas were excluded as controls, as were those in whom cancer or IBD was found at endoscopy.

The mean (SD) age of UC patients, 48.8 (13.8) years, was different to that of controls, 51.9 (15.5) years. Sex distribution of 79 m/71 f in UC, 90 m/115 f 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 18 (12%), proctitis in 12 (8%).

Only 6 UC patients had ever had dysplastic polyps. 2 had a single adenomatous polyyp proximal to the colitis segment. 4 patients had dysplastic polyps within the colitis segment. 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 least 1 adenomatous polyp, χ² = 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, χ² = 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 colitc 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 predeter-mined 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 pericolic 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 pericolic 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 pericolic fat may be important prognostic factors.
Conclusions: The majority of patients would accept alternative methods of monitoring their condition while maintaining links with their supervising specialist team. The provision of personal weighing scales would permit home monitoring for all. There are potential benefits to both patient and our overburdened GI services by adopting alternative methods of follow up.

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: 25,623 men and women aged 45–74 years in Norfolk (UK) 2,993 men and women aged 35–64 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=0.9–7.6), sugar OR=1.8 (95% CI=0.5–5.3), fat OR=1.6 (95% CI=0.5–3.3). A higher fish consumption appeared to protect against the development of ulcerative colitis (lower vs middle tertile OR=0.5 (95% CI=0.1–2.5) vs 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 to make 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 assessments of smoking 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 (day, evening, night) compared with normal 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 predictor 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 1.1–6.8]).

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 sulphhydryl 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 < 2mg/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 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). 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.

Conclusion: 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 frequency 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 were reviewed. Staining for colonic metaplasia was undertaken. In 3/15 disease became milder more proximally in PPI and CD cases. In 3/15 disease became milder more proximally in PPI and CD cases. In 3/15 disease became milder more proximally in PPI and CD cases.
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 score worse than −2.5 at any site, osteopenia as a T score 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 table 1). Conclusion: NOD2 mutations associated with Crohn’s disease do not appear to contribute to the incidence of osteoporosis in this condition.

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 TNFα antibody, Infliximab offers an alternative to current medical therapy in CD with two thirds of treated patients responding. There are however concerns regarding potential immunogenetic and immunosuppressive effects. TNFα promoter polymorphisms at positions −1031, −863, −857 and −308 have been associated with increased transcription and production of TNFα and may therefore influence response to this agent.

Aim: To determine whether polymorphisms in the TNFα and lymphotoxin alpha (lta) genes can predict response to Infliximab.

Methods: 3 LTA (+A720G, +C365G and +G249A) and 7 TNFAa (−1031C, −863A, −857A, 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 site, osteopenia as a T score of < −2.5 at any site.

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: 103-1013C 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 TNF1031C observed in Stage 1 is likely to represent a Type 1 error. Alternatively the failure to replicate this genetic association may due to clinical differences between centres in the selection of patients offered Infliximab.

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 vitamind, which has antiproliferative properties. VDR polymorphisms may confer increased risk of Crohns Disease (CD). This study tests the hypothesis that the Taq1, Fok1 and Apa1 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 Apa1 single nucleotide 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 was 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.

THE PREVALENCE OF GUT TRANSLLOCATION 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.
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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-β (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-β results in upregulation of mucosal expression of TGF-β1 in IBD tissues compared with ED alone.

**Method:** Three liquid formulae were used: (1) ED (EQ28, SHS Ltd, Liverpool) with addition of bovine colostrum rich in TGF-β (0.9mg TGF-β per 100gm colostrum) (ECO); (2) ED with addition of whey enriched with TGF-β (300mg TGF-β 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 Warmsay 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 BrD-uptake. Immunohistochimical 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 molar TBS, pH 7.6). Crypts and epithelial surface staining was quantified with a Video-Image-Analyser 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.

**Results:** 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 (29.41±4.0, p<0.009) 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±1.4, p<0.01), 1:5 (33.11±1.8, 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 ECO 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.

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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 and its localization. UC and CD diagnosis was based on standard criteria. Disease activity in CD was evaluated by using the CDAI score and in UC by the simple clinical colitis activity index. Standard laboratory parameters including red and white blood cell count, haemoglobin, haematocrit, platelet count, albumin, erythrocyte sedimentation rate and C-reactive protein (CRP) were routinely determined in all patients.

**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 levels 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.

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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. However, the pro-inflammatory roles of Al, Si and Ti are unclear. Other elements such as chromium are strongly granulogenic.

**Aim:** 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 quantified 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+ vs [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 intestine. In addition compounds of chromium by EDAX were identified in the inflamed human intestinal mucosa. The percentage of inorganic microparticle-laden macrophages were [means(SE): 70.4 ± 2.40 Vs 50.5 ± 1.3 in Crohn’s, UC and controls. The area [%±SE] of mucosa occupied by macrophages were: 6.3±0.3 % ± 4.2±0.2 % ± 2.4±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 as well 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.

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PATHOGENESIS OF INCREASED BONE TURNOVER IN INTESTINAL INFLAMMATION

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**Background:** Intestinal bowel disease is associated with osteoporosis. The aetiology is not clearly understood and may include steroid treatment, reduced calcium intake, inflammatory cytokines and undernutrition.

**Aim:** To determine the relative contribution of undernutrition and inflammation to increased bone turnover in a model of colitis.

**Methods:** Wistar rats (n=42) were divided into 3 groups: 1) healthy controls, 2) colitis and 3) pair-fed (PF, healthy animals whose daily food intake is matched to the colitic group, thus separating the effects of undernutrition from inflammation). Colitis was induced by intrarectal administration of trinitrobenzenesulphonic acid (TNBS) in ethanol. At day 5, trunk blood was collected for measurement of osteocalcin (marker of bone formation) and pyridinoline cross-links (PYD, marker of bone resorption) and the colon removed for assessment of severity of inflammation by measurement of myeloperoxidase (MPO). The right tibia was removed for measurement of bone mineral density (BMD).

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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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**CO-EXISTENT FUNCTIONAL DYSPESIA (FD) IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS) WORSENS EXTRA-INTESTINAL SYMPTOMATOLOGY AND QUALITY OF LIFE**

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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).

Results: 52 (65%) of patients with IBS had co-existent FD (IBS FD), whilst 45 (58%) of patients with FD had co-existent IBS (FD IBS). Patients with IBS FD reported a greater number of EI symptoms [29(19,22)] (P=0.001) than those with FD [17(15,19); P=0.06], IBS only [13(10,16]; P<0.001] or FD only [17(14,19); P=0.08]. In addition, patients with IBS FD had a poorer QOL [28(23,25.5, 31.2)] than those with FD [35.2(31.9,38.4); P=0.02] but not compared with those with IBS [32.4(29.3,36.5)] or IBS only [33.4(30.2,36.5)]. Interestingly, poor QOL correlated with the number of EI symptoms reported in all patient sub-groups [IBS o.r=0.562, FD o.r=0.582, IBS n=0.568, FD n=0.469; P<0.01]. Furthermore, FGID symptom severity correlated with both the number of EI symptoms and poor QOL in patients with IBS FD [r=0.573, P<0.001; r=0.333, P=0.017, respectively] & FD [r=0.309, P=0.39; r=0.352, P=0.019] and IBS [r=0.392, P=0.035; r=0.333, 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.

**USE OF OVER THE COUNTER MEDICATIONS AND ALTERNATIVE THERAPIES IN COMMUNITY BASED IBS “VOLUNTEERS”**

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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 table below). 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.

Financial support for this study was given by Glaxo Smith Kline. *Smith, G.D & Penman, I.D, Gut [2001]; **48 (suppl II): A45.

**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 subjects are scanty and the relationship between lactose intolerance and post-infectious IBS is still debated.

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 antibiotic 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 intolerance.

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<table>
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<th>Controls</th>
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<tr>
<td>Osteocalcin (ng/ml)</td>
<td>60.9±16.1</td>
<td>33.3±5.9*</td>
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<tr>
<td>PYD (mmol/l)</td>
<td>1±6.54</td>
<td>2.5±0.7**</td>
</tr>
<tr>
<td>BMD (mg/unit vol)</td>
<td>789±28</td>
<td>687±66†</td>
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</table>

*P=0.002; **P=0.0005; †P = 0.02 vs controls.

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<table>
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<th>Drug taken</th>
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<th>OTC (n=146)</th>
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<tr>
<td>Alter gut motility</td>
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<td>Anti-diarrhoeal agents</td>
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</tr>
<tr>
<td>Aloe vera</td>
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</tr>
<tr>
<td>Herbal remedies</td>
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<td>22</td>
</tr>
<tr>
<td>Others</td>
<td>47</td>
<td>18</td>
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**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 currently takes amitriptyline, lactose intolerance cannot be said to be present. 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:** We therefore assessed tissue 5-HT levels in the gastrointestinal tract (GIT) in fed and starved rats.

**Results:** Male and female Wistar rats were fed standard rat chow or starved for 24h (200g, total n=24, six in each group). The rats were sacrificed by cervical dislocation and the GITs dissected out and frozen in sections immediately in liquid N2. The GITs were divided into stomach, duodenum, small bowel, proximal and distal colon. Frozen sections were weighed and fragmented using a mortar and pestle and a weighed portion placed in 1ml of 10% v/v perchloric acid (PCA). PCA samples were homogenised using an ultraturrax and spun at 12,000 rpm for 15 min. The resulting supernatant was analysed by HPLC with fluorimetric detection. The results expressed as concentration of 5-HT in each section by pmol/mg dry weight (dw).

The remaining tissue was placed in a drying oven for 18 h to determine wet weight/dry weight ratio. Data was assessed using Mann Whitey (StatsDirect programme; significance level p<0.05).

**Results:** No differences were detected between male and female 5-HT concentrations in the GIT but fed rats had significantly less 5-HT in the stomach than starved rats (mean 78.7 pmol/mgdw (lower 95% CL 65.4: upper 95% CL 92.1) vs mean 142.9 pmol/mgdw (lower 95% CL 65.4: upper 95% CL 92.1) p=0.02). Fed male rats had significantly less 5-HT in the stomach than starved rats (mean 78.7 pmol/mgdw (lower 95% CL 65.4: upper 95% CL 92.1) vs mean 142.9 pmol/mgdw (lower 95% CL 65.4: upper 95% CL 92.1) p<0.05).

**Conclusion:** Quantitative differences detected between 5-HT in the stomach of fed and starved rats may be involved in the effect of feeding on postprandial symptoms in functional gastrointestinal disorders.

**303 SMOOTH MUSCLE CELL CHOLINERGIC DENERVATION HYPERSENSITIVITY IN HUMAN SIGMOID DIVERTICULAR DISEASE**

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**Background:** Abnormalities in colonic wall support tissue, in particular smooth muscle, may be responsible for diverticular disease (DD). We have used a new indirect immunohistochemical (IHC) technique for quantifying cholinergic activity, together with IHC quantification of type 3 smooth muscle muscarinic (M3) receptors and in-vitro pharmacological experiments, to examine smooth muscle cholinergic activity in DD.

**Methods:** IHC/ image-analysis quantification of Choline Acetyl Transferase (ChAT), co-localised with Protein Gene Product (PGP: a marker of total neural tissue) and smooth muscle M3 receptors, was performed on multiple histological sections of sigmoid colons from eight patients [4 DD, 4 controls] following anterior resections for rectal tumours. Isotonic organ bath experiments were used to examine muscle sensitivities to exogenous acetyl choline.

**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 acetyl choline (DD: EC50 range 0.15–12µmol, median 4.0. Controls: 0.4–5.5, median 1.7)**. 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 acetyl choline (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% v 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**

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**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 anti-depressants (17 %).
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 randomised order. Automated data analysis was performed using a validated software programme. Postprandial activity was analysed using a 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), freq (p=0.002) and amplitude (p=0.001) compared to controls. These differences were significant throughout the postprandial period except in the third hour where the difference in amplitude 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.

THE EFFECT OF PROTEIN, CARBOHYDRATE AND FAT RICH ISOCLORIC MEALS ON POSTPRANDIAL SMALL BOWEL MOTILITY IN IRRITABLE BOWEL SYNDROME (IBS) PATIENTS

S. Zar, F.D. Castillo, A. Grundy, M.J. Benson, D. Kumar. St George's Hospital Medical School, London, UK

Introduction: Whilst abnormalities in fasting small bowel motility in IBS patients have been well characterized, little is known about the fed response in these patients.

Aim: To study the motor response to isocaloric fat, protein and carbohydrate rich meals in IBS patients and healthy controls.

Methods: 19 IBS patients (2M/17F; 10 constipation predominant (C-IBS), 9 diarrhoea predominant (D-IBS)) and 4 healthy controls (2M/2F) were studied. Ambulant small bowel motility was measured using a solid-state flexible catheter positioned in the proximal jejunum. Each subject ingested the three isocaloric test meals (high fat, protein and carbohydrate) in a random order. Automated data analysis was performed using a validated software programme. The postprandial motility index (MI) and contractile frequency (freq) were calculated for two 60-minute epochs.

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 hour. 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 and carbohydrate rich meals. The IBS patients show an increased postprandial 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.

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 Bristol 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 ± 1.9 hr after administration (p<0.05). Bowel movements were 3.2 ± 0.9 times/day before, 1.4 ± 0.5 times/day after administration (p<0.05). The Bristol scale score was 4.2 ± 0.7 before, 3.8 ± 0.4 after administration (p<0.05). Constipation type: Mean colonic transits were 48.8 ± 32.8 hr (Mean ± SD) before administration of calcium polycarbophil, 35.4 ± 37.9 hr after administration. Bowel movements were 2.1 ± 0.4 times/week before, 4.0 ± 1.9 times/week after administration (p<0.05). The Bristol scale score was 1.9 ± 0.4 before, 3.3 ± 0.7 after administration (p<0.05).

Conclusion: Calcium polycarbophil is useful in improving colonic transit in diarrhea and tends to accelerate colonic transit in constipation. Bowel movements and stool type were improved in both conditions.

ALOE VERA LIQUID MAY IMPROVE SYMPTOMS IN IBS RESISTANT TO CONVENTIONAL TREATMENTS

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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 antispasmodics 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 Whoorlaw (APT 1997) was used to detect change in symptoms. The primary endpoint was a response to...
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 deprived 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/10^11 platelets (343,863) ng/10^11 platelets, mean (95% CI); plasma: 5.60 ng/ml (3.84,7.72) ng/ml) respectively. People with a prior FGID had higher consequence scores than those without. People who developed a prior FGID and also in those who go onto develop a FGID had higher consequence scores than those without. People who developed a FGID after gastro-enteritis had significantly more symptoms relating to their gastro-enteritis, think or metabolism (females: 1.50(1.06,1.94) v males: 1.84(0,94,2.74), p=0.002). In addition, increasing age correlated with increased turnover in females (r=0.49, p=0.05) but not in males (r=0.301, p=0.035) but it is of interest to note that the maximum 5-HT turnover in women (upper 95% CI = 1.94) still just reached the mean value (1.84) for male turnover.

Conclusion: Healthy females appear to have reduced turnover of 5-HT compared with males, which may play a role in their increased propensity to develop IBS. However, with increasing age, females appear to increase their ability to turnover 5-HT supporting the observation that changing the ovarian steroid hormone level may affect the 5-HT system.


312 MODULATION OF THE HUMAN SWALLOWING MECHANISM BY THERMAL AND CHEMICAL STIMULATION IN HEALTH AND AFTER BRAIN INJURY

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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 alter swallow physiology. Our aims were to explore the effects of thermal [cold] and chemical [citrus] alterations on the performance of water swallowing in health 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 inappropriate 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?
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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 reaudited.

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 15.3yrs, range 36 – 98), M:F =27:22. Indications for PEG: CV/CNS disorders =27%, pre-op. ENT 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.

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?
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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% marasimic-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 group (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 insertion. 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.

317 POST-PYLORIC NASOJEJUNAL TUBE FEEDING IN CRITICALLY ILL PATIENTS
J.R. Boulton-Jones, J. Lewis, J.C. Jobling, K. Teahan. Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

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 parental feeding prior to NJT feeding. The commonest indications for the use of NJT feeding were reduced oral intake during chemotherapy (24 patients), gastro-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. 7 were discharged to another hospital. 11 patients had NJT feeding continued for a median of 11 days (range 0–180 days).

Conclusion: 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.

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318 FISH OIL REDUCES PGE, 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 (ArA) 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 reduce 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 regimes 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.

319 THE NASAL LOOP PROVIDES AN ALTERNATIVE TO PEG IN HIGH RISK DYSPHAGIC STROKE PATIENTS
M.R. Anderson, M. O’Connor, J. Woodward, D. Mayer, K. Kane. Selly Oak Hospital, University Hospital Birmingham, UK

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.

Introduction: Nasogastric tubes (NGT) in dysphagic stroke patients that can be per-
formed under light or no sedation. A loop of tape is passed round the nasal septum and this secures the NGT in place.

Methods: A six month prospective audit of 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.

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 NL 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.

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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

Methods: Design: Prospective, open 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 percussion by a trainee or consultant. The actual biopsy site was then determined using US by a single operator (trainee) in the same sitting. US examination.

Results: Between 2–6 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, randomised 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 setting. 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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Aims: To determine the accuracy of endorectal ultrasound and the intra and inter observer variation in the preoperative staging of rectal cancers between the specialities.

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 of ultrasound images, 1 observer (R1) staged 16 out of 31 cancers accurately, whereas 1 observer (R2) staged 7 out of 31 cancers accurately. 1 observer (S1) staged 25 out of 31 cancers accurately, whereas 1 observer (S2) staged 20 out of 31 cancers accurately. Between R1 and R2, there was a perfect intraobserver agreement in staging rectal cancer. Between S1 and S2, there was moderate intraobserver agreement. Between R1 and S1, there was good intraobserver agreement.

Conclusions: 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

S. Moreea, G. Naylor, C.L. Kay1, C.G. Beckett. Department of Gastroenterology and Radiology, Bradford Royal Infirmary, Duckworth Lane Bradford BD9 6RJ, UK

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 133 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 endoscopic/radiological approach.
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326 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.

Methods: Data was obtained from clinical, pathology, dietetic and GP records in the area. Approval was given by Bro Taf 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 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.

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.

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<td>Children</td>
<td>8</td>
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327 THE HLA ASSOCIATION OF COELIAC DISEASE: AN INVESTIGATION OF UK PATIENTS WITHOUT THE COMMON DISEASE ASSOCIATED DQ2 GENOTYPE

S.J. Moodie, J.S. Fraser, A.L. King, E. Kontides, H.J. Ellis, P.J. Ciliate. Gastroenterology, St Thomas Hospital, Kings College, London, UK

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. DQ8 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 DQ8 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 DG8 positive. 40% of DG8 haplotypes in DQ2 negative coeliacs carried the DRB1*0404 allele, 30% the 0401 allele, 15% each 0402 and 0404 respectively. Of the 5 DG2 and DRK4 DG8 negative coeliac, 4 carried one half of the DQA1*0501,
HYPERSplenISM IN COELIAC DISEASE: IS PROPHYLAXIS NECESSARY?

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Background: It is recognised that coeliac disease and ulcerative colitis are associated with hypersplenism. Pneumococcal prophylaxis for these patients is not normal practice at our hospital but despite this paucity of experience suggests that coeliac patients rarely suffer from severe infections. However, a recent Drugs and Therapeutics Bulletin suggested that these patients should be vaccinated to reduce the risk of pneumococcal sepsis. Therefore we decided to assess the current practice of gastroenterologists in the UK.

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 hypersplenism 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 sepsis and coexisting immunocompromise were commented on as distinguishing features.

Ulcerative colitis: 6% (n=13) of respondents assess ulcerative colitis patients for hypersplenism. Five of these do not treat this hypersplenism. If treated these patients receive pneumovax alone (4) or a mixture of pneumovax and longterm 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 hypersplenism. As a questionnaire survey it is open to bias and refinement of practice is recommended.

CTLA-4/CD28 SUSCEPTIBILITY POLYMORPHISMS MAY BE DIFFERENT IN COELIAC DISEASE TO THOSE PREDISPOSING TO TYPE 1 DIABETES AND GRAVES’ DISEASE

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Background: We previously demonstrated association of coeliac disease (CD) with a locus on chromosome 2q33, containing the cytotoxic T-lymphocyte associated (CTLA-4) gene and the CD28 gene. Association has also been demonstrated in other populations. However the precise aetiological polymorphism is still not known. CD is associated with autoimmune disorders including type 1 diabetes (T1D) and Graves’ disease (GD). These conditions also demonstrate association with 2q33, and the strongest association has recently been demonstrated with two single nucleotide polymorphisms close to the CTLA-4 gene: MH30 (23327G>C) and CT60 (6230G>A) (unpublished data).

Methods: 149 affected individuals and 149 unaffected controls were genotyped for MH30 and CT60 with CD.

Conclusions: We found that MH30 and CT60 are associated with coeliac disease. Previous studies have compared coeliac disease with type 1 diabetes and Graves’ disease, but this is the first study to compare coeliac disease with MH30 and CT60. Haplotype frequencies were also almost identical in both case and control groups. Absolute allele and genotype counts were compared with the 149 affected individuals using 2x2 and 2x3 contingency tables respectively.

EARLY IDENTIFICATION OF WHITE CAUCASIAN PATIENTS WITH COELIAC DISEASE: ARE AUTOANTIBODIES USEFUL?: A COMPARISON OF AUTOANTIBODIES IN SOUTH ASIAN AND WHITE CAUCASIAN COELIAC PATIENTS

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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 coeliac patients.

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 type 72 Caucasian and 18 South Asian coeliac patients.

Results: The HLA class I alleles were very similar in Caucasian and South Asian CD patients. HLA-B*08, A*03 and DQB1*02 alleles were significantly more frequent amongst the South Asians, (P<0.0001, 0.002, <0.0001 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-B*08 and DRB1*03 alleles were similar between the groups. The HLA-A*01, B*08, DRB1*03 and DQB1*02 haplotype combination was seen in 63.5% 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 stronger determinants of CD susceptibility in South Asians compared to Caucasians.

TROPICAL ENTEROPATHY: A DYNAMIC RESPONSE TO ENVIRONMENTAL INFLUENCES

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Background: Small intestinal mucosal architecture, absorptive capacity and permeability differ in tropical and temperate populations, but their dependence on environmental factors has not been established in indigenous (as opposed to migrant) adults.

Aims: To assess variability of jejunal architecture and function over time and their responsiveness to environmental influences.

Participants: Adults (n=202) resident in a small part of one impoverished township in Lusaka, Zambia living under conditions of high exposure to enteropathogens.

Methods: Jejunal biopsy and four-sugar absorption/permeability measurement annually in each of 3 consecutive years; morphometry of villous and crypt compartments.

Results: All biopsies showed macroscopic enteropathic changes. Permeability was higher in younger women, and in HIV seropositive adults. Structural and functional measurements were only weakly correlated with each other and did not show parallel correlations with intestinal infection, nutrition, or HIV stage. HIV seropositive participants tended to show a progressive reduction in villous height. There was a high degree of variability over time between individuals, with a majority changing significantly from one year to the next. In the group as a whole there was a 15–20% seasonal variation in villous height.

Conclusions: In this tropical population, the jejunal mucosa is dynamic and responsive to environmental influences. Architectural and functional measurements do not predict each other but are complementary.

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 (GMI, 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.

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Median symptom Score</th>
<th>Median hydrogen (total) (ml/24 hrs)</th>
<th>Median hydrogen (breath) (mls /12hrs)</th>
</tr>
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<tr>
<td>Standard diet</td>
<td>6 (IQR 2 - 7)</td>
<td>285.8 (IQR 151.4-434.2)</td>
<td>19.7 (IQR 1.8-36.9)</td>
</tr>
<tr>
<td>Gluten free diet</td>
<td>1 (IQR 0.5-1.5)</td>
<td>91.6 (IQR 71.3-140.)</td>
<td>20.9 (IQR 7.45-25.8)</td>
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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

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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 regulate 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 an ex vivo organ culture of treated CD biopsies the effect of a JAK/STAT1 inhibitor on the gliadin-mediated induction of costimulatory molecules was examined.

Results: High IFN-γ and a more pronounced phosphorylation and DNA-binding activity of STAT1 were seen in CD in comparison to controls. By immunohistochemistry, STAT1 was localised within the nucleus of epithelial and lamina propria cells. Staining was more intense and diffuse 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 morphology 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 morphology 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 and 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 SI 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 proposed 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=0.004) and association (p=0.039). Pooling these findings with published analyses through a meta-analysis showed significant evidence for linkage (p=0.0008) and association (p=0.0006). Mutational analysis of both CTLA4 and CD28 did not show any disease-causing mutations.

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 of the non-HLA linked inherited susceptibility.

P337 ROLE OF TRANSCRIPTION FACTOR NF-κB IN CYCLOOXYGENASE-2 PROMOTION INDUCED BY HELICOBACTER PYLORI IN ENDOTHelial CELLS

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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 translation of NF-κB. NF-κB 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-κB sites on the COX-2 promoter in H. pylori induction.

A parent 5' flanking DNA fragment (−891/+9) and its NF-κB deletion mutants (−891/+9) were constructed into a promoterless luciferase expression vector pGL3. A proximal NF-κB site mutant (−222 to −213), a distal NF-κB site mutant (−447 to −438), and a double NF-κB mutant were used. Transfected cells BPAEC (vascular endothelial cells) were incubated for 24 hours with live H. pylori (strain 60190, tox+++, cagA−). Firefly and renilla luciferase activities were measured.

Mutation of either or both of the NF-κB 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 v 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 v 0.26±0.03, parent construct with H. pylori v control medium, p<0.05) but this induction was unaffected by deletion of either or both of the NF-κB sites.

H. pylori induces COX-2 in vascular endothelial cells via gene induction. The resultant increased generation of endothelial cell prostanoyl may play a role in modulating 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-κB sites on the proximal portion of the promoter.

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 novel 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.
339 DOWNREGULATION OF αβ INTEGRIN PRECEDES THE INDUCTION OF APOPTOSIS BY BUTYRATE IN COLORECTAL CANCER CELL LINES

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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 μmol/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 the cell lines, which were found less sensitive to the butyrate-induced 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 POLYPOSIS (HPP) ASSOCIATED COLORECTAL CANCER (CRC) PROVIDES EVIDENCE FOR THE SERRATED CRC PATHWAY

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Background: MSI-H occurs in 10–15% sporadic CRC. The precursor is unknown but may be the hyperplastic polycolon (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, undifferentiation 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. MS analysis was performed by PCR at Bat25, Bat 26, Mvcl1, D2S123, APC, D1S221 and D17S250 and compared to genomic or normal tissue DNA. MS status was defined as follows: MSI-H = 3 unstable (>1 mononucleotide marker); MSI-Low (MSL-L) = 1–2 unstable, MS stable (MSL-S) 0 unstable. Tissue samples were analysed by immunohistochemistry for mismatch repair proteins MSH1, MSH2 and MSH6.

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 Craf-like or conspicuous lymphocyte infiltrate. 6/22 (27%) CRCs were MSI-H and were proximal and showed mHMM1 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

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Background and Aims: The non-oxidized precursors of gastrin stimulate proliferation of colonic epithelial cells. Transgenic mice which overexpress human progastrin (hGAS) are more susceptible to the induction of colonic aberrant crypt foci and adenomas by the chemical carcinogen azoxymethane than wild type mice (FVB) and mice which overexpress amiodar (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 (hGAS) and gastrin overexpressing (INS-GAS). All were examined with their wild-type counterparts (FVB and C57BL/6). p21 expression was analysed by immunohistochemistry and Western blotting using a rabbit polyclonal primary antibody.

Results: 4.5h following 1 Gy and 8 Gy γ-irradiation, apoptosis was induced to similar levels in the small intestine and colon cancer crypts of all mice. Colonic mitosis was inhibited to almost undetectable levels by 8 Gy γ-irradiation in wild-type, GAS KO and INS-GAS mice. However, significant mitosis persisted in hGAS mice 4.5h following 8 Gy γ-irradiation. GAS KO mice also showed increased length of colonic crypts compared to FVB and INS-GAS γ-irradiation caused induction of p21 expression to similar levels in hGAS and FVB colonic epithelium.

Conclusions: (1) 4.5h after DNA damage by 8 Gy γ-irradiation, mice with elevated progastrin exhibit significantly higher levels of colonic mitosis than wild-type or gastrin overexpressing mice. (2) Progastrin-induced induction 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, Division of Gastroenterology, University Hospital Nottingham, UK

Introduction: Non-steroidal anti-inflammatory drugs (salicindar derivatives in particular) are useful for prevention of colon cancer. Earlier reports describe inhibition of palmitate β-oxidation by NSAIDS and demonstrate that elevated cellular arachonate levels cause apoptosis.

Methods: We hypothesised that inhibition of β-oxidation of arachonate would lead to arachonate accumulation and possibly cell death. We determined effects of NSAIDS on palmitate and arachonate β-oxidation and cell viability. HCT-116 cells were grown to confluence on 24-well cluster plates and were incubated over 2 hours in DPBS with 1H-palmitate or 1H-arachonate (100µM, at 42 and 48 dpm/mole respectively) in the presence of defatted BSA (1.2mg/ml). β-Oxidation rates were measured by 1H-water production. NSAIDS including indomethacin, sulindac sulphide (SS), sulindac sulphide and ibuprofen (0–1000µM) and a patinol carnitine transferase-1 inhibitor (etomoxir 10µM) were incubated in DPBS containing defatted albumin for 45 min prior to 2hr incubation of chemicals with 1H-palmitate or 1H-arachonate. 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-arachonate 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-arachonate β-oxidation at concentrations up to 500mM. Results represent mean +/- sem of 10-12 replicates. (n=4). See table.

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**HY-palmitate**  **HY-arachidonate**  **viability**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tr>
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<td>85 ±/− 3.4</td>
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<td>Indomethacin</td>
<td>251 ±/− 15</td>
<td>140 ±/− 15</td>
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<tr>
<td>Sulindac naproxen</td>
<td>775 ±/− 16</td>
<td>561 ±/− 32</td>
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<tr>
<td>Ibuprofen</td>
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</table>

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 vasculature in association with H. pylori infection. We have previously shown that certain strains of H. pylori induce platelet aggregation via the platelet glycoprotein GP Ib. The GP Ib 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 [4x10^9 CFU/ml] were added to 50µl of polyclonal anti-vWF antibody or a monoclonal anti-vWF 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 FACSCalibur flow cytometer. H. pylori strain 60190 bound anti-vWF antibody [mean fluorescent intensity: polyclonal anti-vWF 324±75 and 1124 for control; monoclonal anti-vWF 525±4 and 10±1 for control]. However, the non-aggregating strain J104 showed reduced binding of the polyclonal anti-vWF antibody [strain J104: Geometric mean 22±19; strain 60190: Geometric mean 223±23; p=0.005, n=3, t-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-vWF 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 GP Ib. 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.

APOTOTIC PATHWAYS OF DETACHMENT INDUCED CELL DEATH IN ISOLATED HUMAN ENTEROCYTES

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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 grow in culture are complex, but the single most important factor is that cells die from detachment-induced cell death (DICC) 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 (BD Bioscience), after which time they were smashed 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 assaying surface expression of phosphatidylserine (PS) using flow cytometry and by DNA ladder- ing. Activation of the apoptotic proteins poly(ADP-ribose) polymerase (PARP), BH3 interacting domain death agonist (BID), caspase 3, caspase 8 and caspase 9 were assayed by Western blotting.

Results: Detachment treatment of human duodenal biopsies produces a pure, non-apoptotic population of enterocytes. Isolated enterocytes undergo rapid DICC as assessed by surface expression of PS and DNA laddering. DICC 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. DICC can be delayed but not halted by the addition of the broad spectrum caspase inhibitor (Boc-D-FMK) and the selective caspase 8 inhibitor (ZIETD-FMK).

THE IMPACT OF ALGINATE BIOPOLYMERS AND EPIDERMAL GROWTH FACTOR ON FLUID PHASE ENDOCYTOSIS

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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 precursor 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. Alginate biopolymers are widely used in the treatment of gastroesophageal reflux disease (GORD) and impart a coding change. The different allelic forms were relatively common and were all expressed in duodenum. No relationship was found between these haplotypes and the level of RNA expression.

To be able to investigate the control of gene expression, we determined the nucleotide sequence of 939bp of the ECaC2 gene upstream from the translation initiation site, comprising the 5'-UTR and the promoter. No classical TATA-box is present, but a number of other potential transcription factor binding sites can be identified, some of which are conserved in the mouse gene. A consensus vitamin D-response element in the mouse gene is deleted in the human sequence.

These studies into the mechanisms governing expression of ECaC2 gene products in human duodenum will enable progress in the understanding of the molecular factors affecting calcium absorption.
H120L has the greatest impact on FPE. All batches of H120L have a similar impact on FPE.

**Conclusions:** The results presented here indicate that we are gradually unravelling the properties of alginete biopolymers and how these properties impact on FPE. This in turn may lead to improvements in medications aimed at the treatment of oesophageal disease.

### Glycine-extended Gastrin Can Promote An Increase in Pro and Active MMP-2 Expression at the Protein Level in Cells

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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 classical CCK-2.

**Methods:** Gelatin zymography 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^{-10} M) and or the addition of 3 different CCK-2 receptor antagonists (YM022, JB95008 and JMV1155). The cell lines investigated were: human fibrosarcoma HT1080 transfected with MM1-MMP, and the mouse fibroblasts 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. Over expression of various matrix metalloproteinases (MMPs) has previously been speculated to correlate with tumour progression in a variety of cancers.

**Results:** GlyG17 increases the invasiveness of cells that already express active MMP-2 but has no effect on cells that express only the pro form. The MMPs tested. JB95008 was the only CCK-2 receptor antagonist that significantly reduced GlyG17 increased MMP-2 expression (p<0.05). With the stimulation of GlyG17, only the HT1080 MT1-MMP transfectants had a significant (p<0.05) increase in their matrigel invasion.

**Conclusions:** The results presented here indicate that we are gradually unravelling the properties of alginete biopolymers and how these properties impact on FPE. This in turn may lead to improvements in medications aimed at the treatment of oesophageal disease.

### A Study Into the Relationship Between Epidermal Growth Factor, Its Receptor and Gangliosides G_{a1} and G_{a2}

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**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 G_{a1} and G_{a2} in four oesophageal cell lines, and the impact of gangliosides on RME.

**Background:** EGFR is a 6 kd 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 exposed to fluorescein isothiocyanate (FITC)-labeled gangliosides and were harvested for FACScan® analyses or slide fixed for confocal microscopy. Immunogold technique was employed to analyse the plasma membrane location of EGFR and G_{a1} and G_{a2} by electron microscopy.

**Results:** Confocal analyses indicate colocalisation of EGFR and ganglioside on the cell membrane. FACScan® analyses indicates cell lines with greater expression of EGFR also have greater amounts of ganglioside. 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. Greater amounts of ganglioside are present in squamous cell carcinoma cell line than that of adenocarcinomas. G_{a1} inhibits the mode of action of EGFR in squamous cell carcinoma cell lines but not in adenocarcinoma cell lines.

**Conclusion:** These results provide us with information on the location of both 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 EGFR binds to EGFR, and that G_{a1} acts as a monitor for the binding of EGFR to EGFR.

### Variable Expression of SEP70, a Novel Squamous Epithelial Stress Protein, in Barrett’s Metaplasia

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**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. Animal and human epithelial cells such stressors activate classical heat shock protein responses. This laboratory has previously demonstrated, in human oesophageal squamous epithelium ex vivo, that HSP70 is down-regulated and that SEP70 is up-regulated in response to thermal, ethanol, low pH and glycopeanic 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 SEP70 and HSP70 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 HSP70 and SEP70, 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. HSP70 was present in squamous epithelium. It was, however, variably expressed in Barrett’s samples. SEP70 was expressed in normal squamous epithelium but in Barrett’s tissue urea lysates demonstrated a laddering of SEP70 immunoreactivity to different molecular weights.

**Conclusion:** The laddering of SEP70 immunoreactivity may be due to detection of sub-cyttoplasmic pools. This could reflect selective targeting for ubiquitination 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.

### SODIUM BUTYRATE DOWNREGULATES IGFB-BINDING PROTEIN-3 EXPRESSION IN THE ABSENCE OF DE NOVO PROTEIN SYNTHESIS

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Butyrate, the pleitropic by-product of bacterial fermentation, has known effects on histone acetylation. The upregulation of genes by alteration of nucleosome-DNA interactions via the inhibition of histone deacetylases is a well understood mechanism by which butyrate directly upregulates gene expression. IGFBP-3 is constitutively secreted by intestinal epithelial cells and its transcription is downregulated by butyrate. The aim of this study was to determine whether the inhibition of IGFBP-3 by butyrate was due to an upregulation of an inhibitor of IGFBP-3 transcription or whether it was due to a direct effect at the IGFBP-3 gene.

**Methods:** Caco-2 cell lines were cultured in complete medium (10% FCS) and resuspended in serum-free media 24 hours prior to the addition of 5mM butyrate in the presence or absence of cycloheximide (CHX) for 6, 12, 24, 36 and 48 hours. IGFBP-2 and -3 mRNA transcripts were analysed by Southern blotting of semi-quantitative RT-PCR amplions, IGFBP-3 protein was assessed by Western blotting.

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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 IGFBP3 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-3 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.

ENDOSCOPY POSTERS

352 AUDIT: TO DETERMINE THE QUALITY OF INFORMED CONSENT IN PATIENTS ATTENDING FOR OGD, COLONOSCOPY AND FLEXIBLE SIGMOIDOSCOPY

M.J. Maida, J. Conibear, M.J. Dew. Gastroenterology Department, Prince Philip Hospital, Bryngwynmawr, Llanelli SA14 8QF, UK

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 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. 1. Williams L et al: Gut 2001;48(Suppl 1): A94

353 PROSPECTIVE AUDIT OF 12 MONTH REFERRALS FOR GASTROSCOPY UNDER THE “THREE DAY RULE”: AN INITIATIVE TO REDUCE WAITING TIME FOR SUSPECTED MALIGNANCY

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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 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 means about 1198 Euros per diagnosis of cancer but only 229.5 Euros per “useful” diagnosis (including PUD and oesophagitis).

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.
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 even 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 GP characteristics—identified from the literature). GPs indicated on nine point Likert scales the relative weighting they assigned to the perceived importance of each factor when making referral decisions (very likely refer, likely refer, no influence on decision, very likely not refer, likely not refer, neutral, no influence on decision, very likely refer, no influence on decision, very likely not refer — +4, 0, -4).

Results: The strongest referral drivers in rank order were: a positive routine examination, the presence of dysphagia, symptoms consistent with GI referral guidelines, positive faecal occult blood test, 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.

Variation in reporting of gastroscopies by different endoscopists at a single centre

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Introduction: Gastroscopy is a fundamental investigation for the gastroenterologist. 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 for correct interpretation of gastroscopies.

Methods: An audit was carried out of gastroscopies performed under the open access system or on the joint medical gastroscopy list from January 2000 to September 2001. Using the "Endoscribe" data-base, demographic details, use of sedation, indication for endoscopy and final endoscopic diagnosis were all retrieved and analysed by the colonoscopist. 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.

Results: 2127 gastroscopies were analysed (female 54%, sedated 21%). There was no consistency in reporting the common diagnoses was very variable and the differences between endoscopists were highly significant when analysed using \( \chi^2 \) (see table).

<table>
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<th>Endoscopic diagnosis</th>
<th>Total</th>
<th>Range (%)</th>
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<td>18–60</td>
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<td>Duodenitis</td>
<td>263</td>
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<td>Miscellaneous</td>
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</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.

Much more emphasis must be placed during training and on the correct interpretation of gastroscopies.

Ulcer haemostasis by the heater probe: bigger may not be better

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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 (120J and 160J 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.

Colonoscopic 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 criterion 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 attempts 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.
We give each trainee the programme on a floppy disk with which they maintain and present the progress of training and which gives a graphic, motivating record of achievement over time. Programmes for more rigorous standards can be used by more experienced colonoscopists.

**A NEW METHOD FOR RAPIDLY MEASURING THE FLEXURAL RIGIDITY OF ENDOSCOPES**

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**Introduction:** There is increasing interest in the use of both variable stiffness colonoscopes and thinner “flippier” flexible sigmoidoscopes. We have previously argued (Gut 2001;49:154) that some form of 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 computer-based system has been developed that enables EI to be continuously measured along the entire shaft of an endoscope in ≤30 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 system accurately logged EI data in a fraction of the time (<30 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/OPHATE IN LOWER GI ENDOSCOPY**

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Intravenous benzodiazepine/opioid (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 (COL).

Consecutive patients (42 FS, 72 COL) 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 COL. 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 COL. Three patients undergoing COL required IV as well as gas. Duration, in minutes, of FS (CI 1.2 (0.5–2.9)) and COL (CI 2.9 (0.5–6)) and completion rate (100% FS both groups, and 92% and 88% COL for gas and IV, respectively) was not significantly different between the groups. Patient discomfort using gas is mild for FS and COL, but not as good as when using IV. For both FS and COL, recovery time is significantly shorter using gas. N2O/O2 is effective sedation and analgesia in lower GI endoscopy in the majority of patients.

**NURSE COLONOSCOPY: A REVIEW OF 160 CASES**

M.E. Vance, S.G. Shah, N. Suzuki, C.J. Thapar, C.B. Williams, B.P. Saunders. Wolfson Unit for Endoscopy, St Mark’s Hospital, London, UK

**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 colonoscopy training programme, based on JAG 2001 guidelines, has been developed to assess whether nurse endoscopists can provide a safe and effective colonoscopy service. A review of the first 160 procedures, performed by the nurse endoscopist is presented.

**Aims:** To review the first 160 colonoscopies performed by the nurse endoscopist.

**Methods:** A nurse endoscopist 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 <10mm. 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 pr bleeding (30%), assessment of IBD (15%), altered bowel habit (15%), pain (11%), diarrhoea (9%), anaemia (8%), cancer follow up (5%), polypectomy (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 25mg, midazolam 1.25mg, and buscopan 20mg. Overall findings were normal 70 (48%), IBD 25(17%), adenomas 18 (12%), diverticulosis 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 perform colonoscopy for diagnostic referrals.

**MAGNETIC ENDOSCOPE IMAGING: A NEW TECHNIQUE FOR LOCALISATION OF COLONIC LESIONS**

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**Background:** Precise localisation of colorectal lesions preoperatively directs appropriate surgical management and avoids confusion at subsequent surgery. Colonoscopy can be notoriously inaccurate and therefore other methods must be used to locate lesions. Magnetic endoscope imaging (MEI), a real-time, non x-ray technique for imaging of the colonoscope, may assist in determining the location of lesions found at colonoscopy.

**Methods:** A prospective study was performed to determine the accuracy of MEI for anatomical localisation of the colonoscope tip. The MEI system was used to identify one of four predetermined locations within the colon. Once identified, two endoscopic marking clips were attached to the colonic mucosa and 400–500ml of Urografin® radio-contrast medium injected to produce an air-contrast “enema”. The clips were subsequently localised by plain abdominal x rays, assessed by a single experienced radiologist, blinded to the colonoscopic findings.
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 easily ruled out with other investigations and thus of little clinical importance.

Conclusions: MEI is a reliable and accurate method for determining the anatomical position of the endoscope 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.

352 RELIEF OF MALIGNANT DYSPHAGIA WITH PLACEMENT OF OESOPHAGEAL METAL STENTS: DO THE BENEFITS OUTWEIGH 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. Improvement 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. Muckeree, 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 which would separate as soon as the wire or catheter was withdrawn. A variety of plastic stents and a perfectly fitting s shape was also cut 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 tips to the stent and pusher, some were made with plastic. A friction 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 duodeno-scope 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
C.J. Larkin, A. Workman, R.E. Wright, T.C.K. Tham. The Ulster Hospital, Dundonald, Belfast, N Ireland, UK

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 ERCPs. There was a significant difference in DAP between the two systems. 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 10.3 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 cancer initiative 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 two fold, firstly to assess the relationship between the urgency of the endoscopy, as designated by the gastroenterologist, and the waiting time. Secondly, to determine the relationship of the assessment of the urgency of the procedure with the findings.

In a nine month period, 2584 gastroscopies and 798 flexible sigmoidoscopies were analysed using a computerised record system, enabling the urgency of the procedure to be recorded along with a coded diagnosis. Significant pathology was defined as grade 2 or more severe oesophagitis, Barrett’s oesophagitis, oesophageal or gastric cancer, or peptic ulcer. For flexible sigmoidoscopy this was defined as neoplastic polyps, colorectal cancer, or inflammatory bowel disease.

Results: For upper GI endoscopy 28% were routine, 51% soon, and 22% urgent, the average waiting times were 154 days, 59 days, and 19 days respectively. The proportions of cases in each category and the nerve waiting times 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 oesophagus was found in 1% of both routine and 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).

Conclusion: 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.

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achieving the "two week standard" for suspected upper GI cancers: continuing pain with minimal gain: a retrospective audit

Introduction: Gastrointestinal endoscopy units worldwide 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 and 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 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>24–48 hrs</th>
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<td>Referral-scope time</td>
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<tr>
<td>Within 2 weeks</td>
<td>51/79 (65%)</td>
<td>12/79 (15%)</td>
<td>16/79 (20%)</td>
</tr>
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<td>2–3 weeks</td>
<td>59/79 (75%)</td>
<td>14/79 (17%)</td>
<td>5/79 (8%)</td>
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patient characteristics and general practitioners’ referral decisions for gastroenterology
A. Douglass, P. A. Cann.

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 GPs’ referral decisions with patients presenting with common GI complaints; dyspepsia (D), change in bowel habit (CHB), and rectal bleeding (RB). (2): to examine the prioritisation and pathway of referrals after the initial decision to refer.

Methods: A fractional factorial design was used to construct case studies, of changing variables, to examine the impact of clinical factors, test results, and socio-economic status upon referral decisions. 21 GPs were interviewed about the factors involved in their decisions to refer patients with GI symptoms in the variable case studies.

Results: RB cases were more often referred (61%) than otherwise identical CBH (44%) and D (41%) cases. Males were more often referred than females patients for each main symptom complex. Increased duration of symptoms resulted in increased numbers of referrals for RB and CBH cases, but not for D. Older patients were more likely to be referred for each symptom complex; however, the impact was maximal for patients with a short history of lower GI symptoms. Abnormal blood tests prompted referral, but normal blood tests discouraged referrals for each symptom complex. Socioeconomic status had no impact on referral. Most of the "two week rule" referrals were for RB (27%); followed by CBH (15%) and D (10%). Almost equal numbers of RB and CBH referrals were assigned as urgent; the majority of D referrals were classified as routine. CBH and RB cases were evenly distributed between named consultant and open access. D cases were sent mainly to an open access route (83%).

Conclusions: Key drivers and inhibitors for GP referral have been examined in detail and will inform our development of a direct access booking system. The impact of gender was unexpected. GPs are not taking full advantage of our fast track open access endoscopy services.

Abstract 368

<table>
<thead>
<tr>
<th>Dysphagia</th>
<th>Upper GI</th>
<th>RB</th>
<th>CBH + / -</th>
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<tr>
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<td>69</td>
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<tr>
<td>Total</td>
<td>50 (92%)</td>
<td>485(67%)</td>
<td>212 (60%)</td>
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severity and follow up of coeliac disease as assessed by the Olympus "Zoom" endoscope
R. Badreddin, P. Barrett, L. Hodgson, W.R. Ellis, A.F. Macklon, J.Y. Yiannakou. University Hospital of North Durham, North Road, Durham, DH1 5TW, UK

Background: The Olympus GIF Q240Z endoscope has a x100 magnification allowing a dissecting microscope view of the mucosa. If it can be shown that the endoscope can accurately identify villous atrophy, there would be a number of potential benefits, including: (i) screening and selection of routine endoscopy patients for intestinal biopsy, and (ii) use in the assessment of patients with known Coeliac disease (CD) who have started a gluten free diet.

Methods: An endoscopic scoring system for villous appearance (Z score) was devised after studying patients with known CD, and comparing endoscopic photographs with histological appearances. Z1 = normal villi; Z2 = stunted villi; Z3 = "ridges and pits"; Z4 = flat. Following this, 17 consecutive patients with known CD were studied over an eight month period. Z score was determined by the endoscopist. The pathology analyses by one individual (PB), blind of the
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 was Z3 (mean 2.3). Seven cases were in “group” endoscope 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. Bottrill, R. Farrell. Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK

PEJ insertion was attempted in 17 patients (10M, 7F, median 74 years) and 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 nausea-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. Prophylactic co-amoxiclav was used in eight patients and other combinations of antibiotics in eight. A videocscope 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 bilateral local anaesthetic was administered into the abdominal wall and the jejunum punctured with the trochar from a standard 16 French Gauge Merck Corflo PEG kit. The guide wire passed through the trochar was retrieved with biopsy forceps and the endoscopic imaging was used to assess whether the ASCOT adequately splinted 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. The ASCOT was less stiff (force 0.001) than the Williams split overtube 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.

371 AN AUDIT OF COLONOSCOPY PRACTISE AND LONG TERM FOLLOW UP IN 505 CONSECUTIVE PATIENTS
S. Thomas-Gibson, C.J. Thapar, S.G. Shah, J.C. Brooker, C.B. Williams, B.P. Saunders. St. Mark’s Hospital and Northwick Park Hospital, Middlesex, UK

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: Aims 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.

Results: 505 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 seven weeks (0–56) 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 matched 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 aspiration, six vasaovagals, three polyphymata 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 OVERTUBE FOR COLONOSCOPY
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Introduction: Our group have extensive experience in the use of different stiffening sigmoid overtures in combination with both adult and paediatric colonoscopes (Gut 1998;42(suppl 1):A18 and Gut 1999;46(suppl II:A33). All the overtures were relatively expensive and had the additional disadvantage of not having an air-tight seal to prevent leakage of inflated air and fluid faecial material.

Aims and Methods: To assess in vitro a recently patented inexpensive disposable corrugated overtube 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 floppyest mode. Magnetic endoscope imaging was used to assess whether the ASCOT adequately splinted 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. The ASCOT was less stiff (force 0.001) than the Williams split overtube 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.
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**


**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, and reporting taking BXs. Only-colonoscopies performed by Consultant Gastroenterologists and Specialist Gastroenterology Registrars were used. The Endoscribe programme, set up in the eEndoscopy 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 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/p/carcinoma surveil lance, radiological abnormalities, inflammatory bowel disease, previous ileal TB, pseudomembranous colitis, suspicion of Maltoma. 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%), aphthous 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. Pathmanathan, K. Smith, G. Thompson, H.G. Aner, 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 practice 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 randomized to particular reporting TI BXs. Endoscopies were performed using standard videoendoscopes 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 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 colonoscopic role may help to meet the increasing demand for diagnostic colonoscopy.

**376 IN INCOMPLETE BOWEL OBSTRUCTION, SELF EXPANDING METAL STENTS FOR PALLIATION OF BOWEL CANCER CAN BE DEPLOYED WITHOUT FLUOROSCOPIC IMAGING**

A.A. Saeed1, M.T. Hendrickse2, P. Isaac3, C.J. Shorrocks1. 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 colorectal stenting can be safely performed without fluoroscopic imaging.

**377 ENTERAL STENT PLACEMENT FOR MALIGNANT GASTRIC OUTFLOW OBSTRUCTION: SUCCESSES AND FAILURES**

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**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 needle” 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 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.

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379 RAPID ACCESS UPPER GI CANCER SERVICE (RAUGICS) VERSUS OPEN ACCESS ENDOSCOPY (OAE): IMPACT OF THE "TWO WEEK RULE"

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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 to UGI cancer (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 vs 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.
ASSESSMENT OF AN OPEN ACCESS IN-PATIENT GASTROSCOPY SERVICE
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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 change in 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 where >100 requests had been made in the last year for GI given the mean number of requests in the previous year in each category 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 melena 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 considered appropriate but the value varied (abdominal pain 41%, haematemesis 74%, melena 83%, anaemia 84%, and nausea/vomiting 57%). The eventual diagnosis was achieved at OGD in all patients in 52% (abdominal pain 29%, haematemesis 79%, melena 65%, anaemia 38%, nausea/vomiting 38%).

Conclusion: An electronic open access service is appropriate for patients 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.

GENERAL PRACTITIONERS’ PERCEIVED UTILITY OF A PROPOSED COMPUTERISED DECISION SUPPORT SYSTEM FOR WEB BASED REFERRAL OF PATIENTS WITH GASTROINTESTINAL (GI) DISORDERS
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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 incorportated as algorithms within the software. This communication will present decison-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 [clinical 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 6 point 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 approved by patients (mean 4.53), (iii) facilitating adherence to local clinical guidelines (mean 4.53), (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 GI given the 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.

Conclusion: 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.

GASTRIC BIOPSY: WHERE FROM AND HOW MANY USING THE UPDATED SYDNEY SYSTEM TO EVALUATE GASTRITIS, ATROPHY, AND INTESTINAL METAPLASIA?
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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 recommends 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.

THE APPROPRIATENESS OF A 24 HOUR BLEEDING SERVICE: PROSPECTIVE AUDIT OF GUIDELINES FOR THE MANAGEMENT OF GASTROINTESTINAL HAEOMORRHAGE
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 suspected 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 measure 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
Introduction and aims: Torque steering is now the preferred method of teaching unibod the tortuous sigmoid colon. One of the criticisms of many teaching simulators is that the "feedback" forces are not realistic. One of us [CA] had had extensive previous experience with the use of pressure sensor gloves to estimate the mechanical forces/mechanical work done by female assembly plant workers 1. We decided to see if (a) we could satisfactorily modify the equipment to measure similar forces being applied by an endoscopist's right and left hand during endoscopic procedures (real or simulated) and (b) if so whether these differed depending on the diameter and stiffness of the endoscope employed.

Aims and methods: A single experienced endoscopist (JH) carried out a total of 10 endoscopic procedures (three OGDs, one flexible sigmoidoscopy, and six colonoscopies) while wearing the sensor gloves. Each glove contained 20 calibrated piezoelectric sensors which sent pressure data to a PC fifty times a second. The data were represented both graphically and numerically using specially written software.

Results and discussion: The equipment accurately and reproducibly measured the, at times, quite considerable forces generated by the right hand during torque steering. Right hand torque forces were predictably much higher during lower GI endoscopy than during OGD. Despite the small numbers of patients studied to date, it is becoming clear that during colonoscopy/flexible sigmoidoscopy greater right hand torque forces are required with thin endoscopes compared with thicker ones. We are now looking at the use of Neural Network/Artificial Intelligence methodology to help analyse the data in greater depth. We are confident we can apply the technique to looking at differences between endoscopists and endoscopes during both real and simulated examinations. The research could have implications in the design of instruments and teaching simulators as well as live "hands on" assessment of trainees during endoscopic procedures. 1. Rockall et al: Mechatronica 1997;7:141–57

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 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. Atkin et al: BMJ 2000;320:1504–9

Introduction and aims: Use of a pair of pressure sensitive gloves to estimate the mechanical forces during either OGD or colonoscopy: a pilot study in 10 patients

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Methods: A pilot study was performed to evaluate the feasibility of using pressure sensor gloves (PSG) to assess the mechanical forces applied during OGD and colonoscopy. The study involved 10 patients who underwent endoscopic procedures with the PSG. The data collected included the magnitude and direction of forces applied by the operator during the examination. The study aimed to determine if the PSG could provide useful information for training and quality assurance purposes.

Results: The study demonstrated that the PSG could accurately measure the forces applied during endoscopic procedures. The data collected showed a significant variation in the forces applied by different operators, indicating the need for standardized training and protocols. The PSG also highlighted the importance of operator technique in minimizing injury to the patient.

Conclusion: The use of pressure sensor gloves in endoscopic procedures can provide valuable insights into the forces applied by the operator. This information can be used to improve training, quality assurance, and patient safety. Further research is needed to validate the findings and to develop standardized protocols for endoscopic procedures.
AN AUDIT OF ROUTINE ILEOSCOPY: PROCEDURE TIME AND DIAGNOSTIC YIELD

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Introduction: Ileoscopy is not routinely attempted because of its perceived technical difficulty. We believe routine ileoscopy is useful in quality assurance and it 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 backwash ileitis. Of those without colonic IBD, 904 had ileoscopy and were diarrhoea and/or anaemia. Overall ileoscopy rate (IR) was 67.5%. IR rose progressively to plateau for the past three years at approximately 85%. Twenty-two colonoscopies were excluded from analysis of PT in 259 patients (previous colonic resection=13; impassable stricture=7; incomplete colonoscopy=1; abandoned due to respiratory depression=1). The median PT and interquartile ranges in minutes were as follows: anus to caecum=7 (5–10); total time=17 (14–21.5); caecum to ileum=2 (1–4); and time in ileum=1 (0.5–2). The median length of ileum examined was 10 cm (10–15).

Conclusions: Ileoscopy is the gold standard in the documentation of completeness of colonoscopy. In skilled hands, it is easy, adds only three minutes to the procedure time, and contributes significantly to quality assurance and diagnostic yield.

A SEVEN YEAR OUTCOME OF ENDOSCOPIC LASER THERAPY FOR PALLIATIVE UPPER AND LOWER GASTROINTESTINAL MALIGNANCY IN A DISTRICT GENERAL HOSPITAL

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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), five (16%) chronic obstructive airway disease (COAD), and three (9%) other medical co-morbidities. 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. 38 (59%) were male; mean age of 75 (range 44–88). 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 malignant malignancy when performed in a District General Hospital setting by an experienced endoscopist.

CLINICAL OUTCOME FOLLOWING DEPLOYMENT OF ENTERAL STENTS TO PALLIATE PATIENTS WITH MALIGNANT GASTRODUODENAL OBSTRUCTION: A DGH EXPERIENCE

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Background: The deployment of enteral stents under endoscopic and fluoroscopic guidance has emerged as an effective alternative to palliative surgery for malignant gastric outflow and duodenal obstruction.

Methods: Twenty-one consecutive patients with inoperable malignant (gastric (28%), pancreatic (67%), and metastatic deposit (5%)) upper GI strictures were prospectively studied between April 1999 to October 2001, on an “intention to treat” basis. Twenty-three procedures were performed using the Wallstent enteral prosthesis, implanted per-orally under endoscopic and fluoroscopic guidance. All patients had severe nausea, recurrent vomiting and their obstructions were deemed inoperable. Twelve (57%) were male and nine (43%) female; mean age 71.6 years. Malignant obstruction occurred at the pylorus (19%), antrum (5%), first and second parts of duodenum (66%), third part of duodenum (5%), and anastomotic sites (5%).

Results: 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 biliary 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 distortion caused by the stent. Both were successfully treated, by inserting further co-axial stents to bridge the stenoses. Twelve patients (57%) 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.

ABDOMINAL PAIN FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY

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Aim: Laparoscopic cholecystectomy is the treatment of choice for symptomatic gallstone disease, although little data exists as to the long term ability of the procedure to alleviate the symptoms of patients.
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% (145 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 preoperatively. 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. There 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 antiendomysial 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 full upper and lower GI tract investigation although five patients were diagnosed with carcinoma. No cases of coeliac disease were detected, but only 18% had antiendomysial 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 abdominal pain occurred in 14 patients (youngest 52 years) and isolated dysphagia 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 dysphagia.

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 CANCER

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

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.
**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 chromagen (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 of purified COX-1 and COX-2. COX-2 and p53 positivity was determined as expression by at least 50% of malignant cells in the section. Results were analyzed using a 2×2 table and Chi² testing.

**Results:** COX-2 and p53 positivity was 71% and 44% respectively. The results are shown in the table below. Chi² analysis demonstrated that the frequency of COX-2 positivity was unchanged between p53 positive and negative tumours (Chi² value = 0.88).

**Conclusion:** The rate of COX-2 dysregulation is not altered by p53 gene mutation in gastric carcinoma.

<table>
<thead>
<tr>
<th></th>
<th>p53 positive</th>
<th>p53 negative</th>
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<tbody>
<tr>
<td>COX-2 positive</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>COX-2 negative</td>
<td>6</td>
<td>7</td>
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**Abstract 396**

**A SYSTEMATIC EVALUATION OF THE SIGNIFICANCE OF IMMUNOHISTOCHEMICALLY DETECTED LYMPH NODE MICROMETASTASIS IN LOCALISED COLORECTAL CANCER**

P.J. Arumugam, J. Beynon, A. Watkins, N.D. Carr, I.V. Shah. Singleton Hospital, Swansea, Wales, UK

**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%) 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.
A SEVEN YEAR EXPERIENCE OF MANAGEMENT OF OESOPHAGEAL CANCER

M.A. Yusuf, A.H. Sadozay, Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan

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], 56 lower 1/3, 62 G.O. junction (45 ACA, 34 SCCA, one lymphoma, six miscellaneous).

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 51.8 yrs. 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 48 yrs. 35 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 46.4 yrs, 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 alive (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.

MATRIX METALLOPROTEINASE-2 CONCENTRATION CORRELATES POSITIVELY WITH PATHOLOGICAL TUMOUR STAGE IN PATIENTS WITH ADENOCARCINOMA OF THE OESOPHAGUS OR GASTRIC CARCINOMA

R.E. Lovett1, G.M. Spence1, J. McAllister1, K.M. Mulholland2, A.N.J. Graham1, J.A. McGuigan3, M.C. Regan4, K.R. Gardiner5. Departments of Surgery and Pathology, Royal Victoria Hospital, Belfast, UK

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 and informed consent was given by each participating patient. Fresh tumour samples from neoplasms of the oesophagus or gastric cancer, obtained at the time of surgery, were homogenised and centrifuged and the supernatants analysed for expression of MMP-2 and -9 using matrix metalloproteinase assay systems (Biotrak RPN 2631 and 2634, Amersham Pharmacia Biotech, Buckinghamshire, UK). All tumours were assessed histologically by an independent pathologist. Tumour staging was based on the UICC guidelines (5th Edition). Correlation analysis was undertaken using Spearman’s rank testing.

Results: Tumour samples were obtained from 33 patients with confirmed adenocarcinoma. Total and inactive MMP-2 concentrations correlated positively with overall pathological stage (r² = 0.14, p < 0.05; r = 0.15, p < 0.05 respectively). There was no correlation between MMP-2 and histological parameters such as depth of invasion, vascular involvement, or lymph node metastasis. MMP-9 did not correlate with pathological stage or histological findings.

Conclusions: This study provides further evidence for the involvement of MMP-2 in tumour invasion and metastasis. MMP-2 concentration in diagnostic biopsies from oesophago-gastric cancers may therefore be of benefit in assisting the decision making process regarding the appropriateness of surgical resection.

CHANGES IN MUSCLE UNCOUPLING PROTEIN EXPRESSION IN HUMANS WITH GASTROINTESTINAL ADENOCARCINOMA

Peter Collins1, Chen Bing2, Peter McCulloch3, Gareth Williams3. 1Royal Free and University College Medical School, Rowland Hill Street, Hampstead, London, NW3 2PF, UK; 2Diabetes and Endocrinology Research Group, Department of Medicine, University of Liverpool, L69 3GA, UK; 3Division of Surgery, University Hospital Aintree, Longmore Lane, Liverpool L9 7AL, UK

The mitochondrial uncoupling proteins-2 and -3 (UCP-2 and -3) are proton mediators of thermogenesis and energy metabolism. We obtained skeletal muscle from 12 gastrointestinal adenocarcinoma patients, of whom six had stable weight and six had lost 2–18 kg, and from six healthy controls undergoing elective surgery. We measured mRNA levels of UCP-2 and -3 using semi-quantitative RT-PCR.

UCP-3 mRNA levels were significantly higher in the muscle of 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). UCP-2 mRNA levels did not differ significantly between groups, suggesting that UCP-2 is regulated by a different mechanism in human muscle and may have a different physiological role in this context. Elevations in muscle UCP-3 activity may enhance energy expenditure and contribute to the tissue catabolism seen in cancer associated cachexia. Manipulation of UCP expression may offer new therapeutic possibilities in combating the high morbidity and mortality associated with muscle wasting both in malignancy and other wasting conditions such as HIV.

PROLIFERATION ANTIGEN MIB-1 IN METASTATIC CARCINOID TUMOURS REMOVED AT LIVER TRANSPLANTATION: RELEVANCE TO PROGNOSIS

A.H.G. Davies, A.D. Amaraparak, 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. Histopathologically a failed 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 MIB-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 MIB-1 index of <2% and another group with MIB-1 index >2%. There was a trend for patients with MIB-1 index of < 2% to exhibit a later recurrence (>24 months) as compared to those with MIB-1 index >2%. The sensitivity as regard to recurrence was found to be 85.7% and specificity 71.4%. Those having MIB-1 <2% showed a longer survival than with MIB-1 >2% with a sensitivity of 83.3% and specificity of 62.5%.

Conclusion: MIB-1 antibody staining was found to be a useful method of predicting the prognosis of metastatic carcinoid/neuroendocrine tumours. Thus 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.

METABOLIC THERAPY INHIBITS GENOTOXIC DAMAGE IN REGENERATING INTESTINAL EPITHELIUM

K. Atherton, A.K. Daly, D.H. Phillips, F.C. Campbell. Depts 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 carcinoembryonic bioactivating enzymes (CYP1A1/1A2) using ellipticine or furafylline and/or (ii) promotion of Glutathione S-transferase (GST) enzymes responsible for carcinogen deactivation, by ethoxyquin or oltipraz.
FEW GASTRO-OESOPHAGEAL MALIGNANCIES ARE IDENTIFIED THROUGH TWO WEEK RULE

S. Subramanian, D. Lloyd, A. Poullis, J. Millar-Smith, J.Y. Kang, P.J. Neild, J.D. Maxwell. Dept of Gastroenterology, St. George's Hospital, London SW17 0QT, UK

**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:** Metabolic therapy by antioxidants or CYP 450 inhibitors promote expression and function of P450s and GSTs and reduce adduct formation in regenerating intestinal epithelium.

**Abstract 404**

<table>
<thead>
<tr>
<th>TWR</th>
<th>Non-TWR</th>
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<tbody>
<tr>
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<td>77 (43-89)</td>
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<tr>
<td>Median time to appointment</td>
<td>5 days (1-12)</td>
<td>20 (1-52)</td>
</tr>
<tr>
<td>Median time to diagnosis</td>
<td>13 days (7-65)</td>
<td>15 (2-565)</td>
</tr>
<tr>
<td>Median time to treatment</td>
<td>18 days (1-82)</td>
<td>16 (1-245)</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
Scottish Audit of Gastric and Oesophageal Cancer, UK

The prospective population based Scottish Audit of Gastric-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 the 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 common in Scottish regions 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, 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.

**Abstract 405**

GASTRO-OESOPHAGEAL CANCER IN SCOTLAND

K.G.M. Park for the Scottish Audit of Gastric and Oesophageal Cancer
Scottish Audit of Gastric and Oesophageal Cancer, UK

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**Abstract 406**

THE GASTRIC CANCER 5 (GC5) STUDY: ANTIBODY RESPONSE AND SIDE EFFECT PROFILE OF G17DT 500MCG IN POST GASTRIC CANCER RESECTION PATIENTS

E.J. Dickson, E. Cowan, R.C. Stuart. University Dept of Surgery, Glasgow Royal Infirmary, Glasgow, UK

**Aim:** Gastrin has a trophic effect on gastrointestinal epithelium as part of its normal physiological function, and gastrin 17 in particular stimulates the growth of gastrointestinal (GI) cancer cell lines. The aims of the GC5 study were to determine the anti-gastrin antibody response to G17DT 500mcg [Aphton Corps] and to evaluate patient tolerance at this higher dose.

**Methods:** Gastrin 17 linked to the diphtheria toxoid [G17DT] was administered as a 500mcg intramuscular injection at weeks 0, 2, and 6 to seven patients who had previously undergone potentially curative gastric cancer resection. Appraisal was obtained from the local Ethics Committee. G17DT antibody titres were measured over the follow up period (median 419 days, range 391–463 days). Patients underwent CT scanning for assessment of tumour recurrence on three occasions.

**Results:** All seven patients achieved an antibody response (median 177.2 units, range 33.9–313.7 units) which remained quantifiable in five patients at the end of the follow up period, although the third dose was administered to one patient only. Four patients developed an abscess at the injection site and all seven patients reported minor to severe local side effects (pain, immobility, and tenderness). Based on CT scanning no patients had tumour recurrence during this period.

**Conclusions:** At this dosage schedule G17DT is an effective method of producing a sustained anti-gastrin antibody response at the expense of unacceptable tolerance. However the high dose of 500mcg may be utilised in conjunction with chemotherapy as combination therapy, as the chemotherapy agents are anti-inflammatory and may suppress injection site reactions.

**Abstract 407**

NOVEL METHOD FOR MEASURING NITROSATION POTENTIAL WITHIN LOCALISED REGIONS OF UPPER GI TRACT

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**Background:** Luminal nitration may be important in the pathogenesis of adenocarcinoma at the gastro-oesophageal junction as swallowed saliva is the main source of nitrite entering the acid stomach. We have developed and validated a method employing multialigned digest analysis (MD) probes to measure nitration at this localised site.

**Method:** MD probes were perfused with distilled water at 0.135ml/hr. The recoveries of chemicals relevant to luminal nitrosation i.e. nitrite (NO(2)), nitrate (NO(3)), thiocyanate (SCN(-)), osmic acid (AA) and total vitamin C (TVC) were studied at 37°C at different pH in aqueous solutions and/or gastric juice (GI). Experiments simulating the gastric milieu, when NO(2) intake was in excess of gastric AA secretion and vice versa were performed. For use in human subjects, four MD probes with 1 metre inlet and outlet tubes were secured in individual recesses created in a nasogastric (NG) tube.
Methods: G17DT was administered by intra-muscular injection to 52 patients with gastric adenocarcinoma and 41 patients with pancreatic adenocarcinoma in phase II studies. 28 patients were followed-up and boosted when antibodies fell to <25% of peak values achieved during the main body of the study.

The antibody isotypes following booster administration were examined by an EUSA capture assay and compared to the antibody isotypes generated by the initial dosing schedule.

Results: One patient died of disease progression prior to booster administration and two boosted patients died prior to antibody analysis. Of the remaining patients, eight of the twelve (66.7%) patients with advanced pancreatic cancer and seven of the thirteen gastric cancer patients (53.85%) achieved a higher antibody response following boosting than after the primary three injections.

There was only one adverse event: induration at injection site of the booster that resolved completely within two weeks with conservative management. The antibody isotypes following booster administration changed from a IgG, IgM, and IgA mixture to a predominantly IgG response.

Conclusion: All boosted patients were able to mount an antibody response. This was at least as good as the one following the initial three doses in most patients, and, in a proportion of patients, was greater with few side effects.

Liver posters 410–441

410 URINARY TAURINE AND HIPPOURATE ARE USEFUL MARKERS OF ALCOHOLIC CIRRHOSIS

K. Dobos, P. Ramachandran, J. Sadler, P. Hewson. Liver Cell Biology Laboratory, Department of Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK; "The Department of Chemistry, University of Edinburgh, King’s Buildings, Edinburgh, UK.

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 52.9) 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 quantify 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 0.23 ± 0.06) (p<0.014). If the two values were combined then the results were again highly statistically significant (p<0.000126).

Conclusions: A combination of low hippurate and high taurine excretions is highly significant as a good marker of alcohol cirrhosis and can be a cheap non invasive marker of the disease.

411 HAZARDOUS DRINKING IN HOSPITAL INPATIENTS: STILL COMMON, STILL UNDER DIAGNOSED

E.J. Williams, E. McFarlane, E. Rigney, B. Saward, M.P. Bradley, D. Ray-Chaudhuri, C. Davidson, D. Gleeson. Liver Unit, Sheffield Teaching Hospitals, Sheffield, UK

Introduction: Brief counselling for hazardous drinkers can lead to reduced alcohol consumption, hence detection is important.

Aims: a) To establish the prevalence and detection rate of hazardous drinking in unselected hospital inpatients and b) to ascertain whether, in patients who present with a first episode of decompensated alcoholic liver disease (ALD), opportunities to manage excessive drinking during previous admissions were exploited.

Methods and Results: a) On specific weekdays over a nine month period, all patients aged 30–60 years admitted to the admissions unit under the care of a general physician or surgeon were considered for screening using the Alcohol Use Disorders Identification Test (AUDIT)
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 (92.6%) 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

D. Thorburn1, E.H. Forrest1, E. Spencer1, K. Olen1, G. Inglis1, C. Smith1, E.A.B. McCruden1, R. Fox1, P.R. Mills1. Victoria Infirmary; ‘Gastroenterology Unit’ and ‘Brownlee Unit, Gartnavel General Hospital; Department of Pathology and Department of Medicine, Western Infirmary; Institute of Virology, University of Glasgow, Glasgow, UK

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 patients who had no RAS polymorphism. Patients homozygous for 0 or 1 low expression RAS mutations had stage 0 or 1 fibrosis compared with stage 2 or 3 fibrosis in patients with 2 or 3 high expression RAS mutations. This demonstrated that high expression RAS mutations and low expression RAS mutations influence fibrosis progression. The frequency of RAS mutations did not correlate with stage of fibrosis.

Conclusions: The role of RAS polymorphisms in the progression of liver fibrosis in patients with chronic HCV was demonstrated in this study.

413 THYROID HORMONE (T3) INCREASES THE FUNCTIONAL CAPACITY OF THE INTESTINAL LIVER

R. Malik, A. Ala, R. Toole, H. Hodgson. Royal Free Hospital, Rowland Hill St, London NW3 2PF, UK

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 mls of 50% galactose via the internal jugular vein approach. (2) A 0.5ml venesection was 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 µmol/min as compared to control rats in which the figure was 7.9 ± 0.4 µmol/min (p<0.01).

Conclusion: A 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 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 had not. 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.

<table>
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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 ENDOTOXAEMIA

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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 urinal excretion of enterically administered 14C-EDTA.

Aim: 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 amebocyte 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 correlation with bilirubin or alanine transaminase. There was no correlation with bilirubin or alanine transaminase. There was no correlation with bilirubin or alanine transaminase.

Conclusions: Genetic screening would detect many thousands of healthy subjects in S Wales. Of the 1% likely to be diagnosed with HH currently 45% will have moderate to severe iron overload based on estimated body iron load (≥4g iron).

1% OF ADULTS HOMOZYGOUS FOR THE C282Y MUTATION OF THE HFE GENE HAVE BEEN CLINICALLY DIAGNOSED WITH IRON OVERLOAD: EVIDENCE FROM THE SOUTH WALES HAEOMOCHROMATOSIS STUDY

C.A. McCune, M. Warwood, L.N. Al-Jader (introduced by A.B. Hawthorne). University of Wales College of Medicine, Cardiff, UK

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 approximately 45% will have moderate to severe iron overload based on established criteria.

THE PREVALENCE OF PORTAL HYPERTENSION (PHT) IN PRIMARY BILIARY CIRRHOSIS (PBC)

E.J. Jones, R. Walter, M.I. Prince, M. Hudson. Centre for Liver Research, University of Newcastle, UK

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 PBC in a comprehensive cohort of patients defined by geographical residence rather than specific clinic 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, endoscopy proven varices and a history of variceal 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 1/1000 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 INTENSIVE CARE UNIT PATIENTS WITH LIVER CIRRHOSIS

C. Chatzikostas 1, M. Roussomoustakaki 1, G. Notas 1, G.I. Vlachonikolis 1, E. Matrella 1, D. Samokas 1, E. Vardas 1, E. Kouroumalis 1, 2, 3

Clinical and laboratory data conforming to the Child-Pugh, 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.

Abstract 416

<table>
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1 Wild type, HHCC; homozygous C282Y, HHYY; homozygous H63D, DDCC, etc.

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.

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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 with CCS was greater 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 identifies a statistically 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 for 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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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 primiparas while 29 had had 1 to 6 previous pregnancies, ten of which were complicated by OC with two associated stillbirth. 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 hyperemesis 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), GLT 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. The interval from diagnosis of OC to delivery ranged from 1 to 142 days (median 8). Uroxycholcholic acid was given to eleven patients with improvement in symptoms in six and biochemistry in ten. Induction of labour or Caesarean section was undertaken in 33 because of OC. There was no maternal or fetal death but 15 of 52 babies required admission to SCBU. Symptoms and abnormal liver function resolved rapidly in 75% within 2 weeks of delivery.

Conclusion: OC complicates 1 in 180 pregnancies in South Wales. It is characterised by elevated transaminases rather than cholestasis; jaundice is neither a necessary nor a common component. Combined medical and obstetric care with early delivery prevents fetal loss.

421 SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA IN CIRRHOSIS: A NATIONAL AUDIT OF THE PRACTICE IN THE UK

C.W.Y. Lai, M. Wardle, V. Birkett, E. Powell, G.A.O. Thomas. Department of Gastroenterology, University Hospital of Wales, Cardiff, UK

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 reply (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 an age limit (median 70) for surveillance. 107/296 (36%) surveyed all cirrhotics 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 unselective 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 decompensation or partial hepatectomy was the primary endpoint. There was no significant difference between the two groups.

Results: Median time to decompensation was 81 months (95% CI, 45-117 months) and was not different between the two groups.
MEASUREMENT OF AFP IN PATIENTS WITH HEPATITIS C CIRRHOSIS DURING HEPATOMA SURVEILLANCE

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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 HCV infection 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 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 commitment 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. Restricting surveillance to US alone would be as effective.

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 10^6. 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.

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. 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. Upregulation 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 overexpression 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 development of cirrhosis.

INFLAMMATION IN MICE WITH LIVER ATROPHY FOLLOWING PORTACAVAL SHUNTING IN RATS

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Background: 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 Prodit 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 (7.43±11.92µm²). Within the PCS group there was a significant reduction in the mean area of hepatocyte nuclei from 55.52±10.34µm² in zone 1 to 45.31±10.68µm² in zone 3 and a marked difference in the mean area of cytoplasm (113.25±51.6µm² in zone 1 to 74.30±42.3µm² in zone 3). Electron microscopy revealed mitochondrial changes in the cytoplasmic organelles in PCS rats in comparison with sham rats. Apoptosis was increased in zone 3 to 2.4±0.3 counts per mm² in PCS rats (P=0.000000) while mitosis was significantly increased in zone 1.

Conclusion: This study shows that liver atrophy after portacaval shunting has a complex aetiology. The microcirculatory disturbances and hormonal changes after portacaval shunting induce apoptosis that further contributes to liver atrophy in this animal model.
ROLES OF TECHNICAL VARIABLES IN EARLY SHUNT INSUFFICIENCY FOLLOWING TIPS FOR THE TREATMENT OF PORTAL HYPERTENSION

1Liver Unit, Department of Medicine, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, Scotland, UK; Department of Radiology, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW, Scotland, UK

Summary: Transjugular intrahepatic portosystemic stent shunt (TIPS) has increasingly been used for the treatment of complications of portal hypertension. This study evaluated the technical predictors of early shunt insufficiency after TIPS placement in patients with advanced liver disease.

A retrospective analysis of 399 patients undergoing TIPS over a period of 9 years between July 1991-July 2000 was carried out. The index technical variables (TIPS) for hepatic, gastric and colorectal varices in both patients, gastric varices in 52, refractory ascites in 42, portal hypertensive gastropathy in 8 and ectopic varices in 9 patients. TIPS placement was successful in 383 (96.0%) patients, and failed in 16 (4.0%). The shunt remained patent without assistance in 40 (10.0%) patients and 44 (11.0%) patients developed early shunt insufficiency within 30 days from TIPS 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 TIPS 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 TIPS were independent predictors of early shunt insufficiency.

Based on our analysis, four technical variables in index TIPS can reliably predict early shunt insufficiency. Total protection from early complications of TIPS 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 antibodies and 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 autoreactivity in disease pathogenesis.

We have recently demonstrated that splenic T-cells from SJL/J mice can be induced to break down both B-cell 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 T-cells in this model.

Female SJL/J mice of 10–12 weeks were sensitised (n=7) with a mixture of murine (m) and bovine (b) PDC (study group). Control mice (n=4) received mPDC only. Mice were sacrificed at 8 weeks post-sensitisation. The spleen was removed and splenic T-cell responses 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 as for splenic T-cells.

The liver infiltrating T-cells from the study group, but not of the controls showed T-cell reactivity with mPDC. Liver T-cells from the study group, but not controls showed a proliferative response to mPDC (study group: mean incorporated counts 6943±2831 V  background 561±2400 p=0.01) derived 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 as for splenic T-cells.

The liver infiltrating mononuclear cell population was isolated by further collagenase digestion and density centrifugation. T-cell responses were characterised as for splenic T-cells.

The liver infiltrating T-cell antigen-reactivity seen in this model closely resembles that seen in human PBC, further confirming the potential value of this model for the study of PBC pathogenesis.

FOCAL LIVER LESIONS: TO BIOPSY OR TO IMAGE?

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Background: There is much debate about whether a focal liver lesion should be biopsied or only imaged, given the risk of tumour seeding in the biopsy track. There is however only anecdotal evidence coming from case reports and small series to support this view. As imaging methods improve, many authors feel that a confident diagnosis need no longer rely on tissue. Practice varies between doctors and strong opinions are held.

Methods: A questionnaire was sent to 73 consultants and SpRs around the region. Four hypothetical cases were given and participants asked to offer a diagnosis, preferred next investigation and whether or not they would biopsy the lesion. The cases included an asymptomatic 60 year old man with a solitary liver lesion, an elderly lady with an apparent colonic liver metastasis, a young woman with a likely pill related adenoma and a middle aged man with a clear hepatocellular carcinoma.

Results: 38 (52%) of those canvassed responded. Several diagnoses were offered for the first case (benign and malignant) but there was more agreement on the initial investigation with CT +/- contrast (83%). There was no agreement on whether to biopsy with 46% saying ‘no’. All respondents gave the correct diagnosis for the case of metastasis and 77% would use CT as the next test. However, only 54% would not biopsy and this figure was significantly higher in teaching hospitals (90% v 40%). Most respondents thought the third case was an adenoma or focal nodular hyperplasia and CT or MRI were the investigations of choice (85%). About half would consider biopsy but this figure was much higher in teaching hospitals (80% v 40%). All participants identified the HCC but there was a large range of next investigations including CT, MRI, biopsy, cytology and angiography. 57% would not biopsy but this figure was higher in teaching hospitals (90% v 44%).

Conclusions: There is a wide discrepancy in biopsy policy between teaching hospital and DGH’s but also between specialties. Significantly, 46% would consider biopsy a metastasis and 43% would consider biopsy an HCC. Without a Grade A evidence base this highlights the need for a large scale randomized controlled trial into management of focal liver lesions with and without biopsy.

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 volume.

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 with a likely pill related adenoma and a middle aged man with a clear hepatocellular carcinoma.

Conclusions: MR guided 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 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 umol/L, normal <14) and borderline in the other 4 (mean 12umol/L). Only one patient became jaundiced (bilirubin 64 umol/L). At presentation serum alkaline phosphatase ranged from 11–150 IU/L (mean 40) and ALT 12–468 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.

432 AN AUDIT OF SPECIALITY MANAGEMENT OF ALCOHOLIC LIVER DISEASE WITH JAUNDICE

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The development of jaundice in the alcohol abuser may indicate acute alcoholic hepatitis (AAH) or the progression to end-stage chronic alcoholic liver disease (ALD). The patients may be cared for by General Medicine (GM) or Gastroenterology (GI) physicians. This audit aimed to identify if there were differences in the treatment and outcome of patients managed in these different contexts.

Methods: Patients with ALD and serum Bilirubin > 80 µmol/l on admission were identified through discharge coding over a period of 27 months (June 1999 – August 2001). Only patients drinking to excess until the two weeks prior to admission were included. Differences in management were identified in the use of corticosteroids (CS), broad-spectrum antibiotics (AB), and nutritional support (N). GI care assumed the patient’s ongoing care for 55% or more of the admission episode.

Results: 79 patients were included in the study: 46 GI, 33 GM. The mean age was 51.6 ± 1.2 years with mean admission serum bilirubin of 230.4 ± 18.4 µmol/l, prothrombin time ratio of 1.57 ± 0.05, and Discriminant Function of 51.4 ± 3.6. The median time to GI review of a patient initially admitted under GM was 3 days (range 0 – 12). Patients managed by GI had a longer median hospital stay (18 [2–87] vs. 10 [2–89] days; p=0.001). Differences in management and 30-day mortality are shown in the table.

Conclusion: Significant differences may exist between GI and GM physicians in the management of ALD patients with jaundice. More aggressive medical therapy may translate into an improved outcome. Speciality triage of these patients should be encouraged.

433 LIVER BIOPSY IN HEPATITIS C: HAVE WE FOLLOWED NICE GUIDELINES?

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Aim: To audit whether patients with hepatitis C undergoing liver biopsy were subsequently treated according to current NICE guidelines.

Methods: Patients with treatment naive RNA PCR +ve hepatitis C undergoing liver biopsy between 1997 and 2000 inclusive were identified using histology and appointment records. Histology was used to categorize the degree of liver disease into mild, moderate and cirrhotic based on a modified HAI scoring (Ishak et al. 1995) and recent BSG management guidelines (Booth et al. 2001). Patient notes were reviewed to assess whether patients received anti-viral treatment by 31st October 2001.

Results: Between 1997 and 2000 113 patients with treatment naive RNA PCR +ve hepatitis C underwent liver biopsy; this constituted 41% of all liver biopsies performed. 38 patients had mild liver disease, 65 had moderate liver disease and 10 had cirrhosis. 8 of the patients with mild liver disease [21%] initiated anti-viral therapy, 3 as part of a UK based clinical trial. 20 of the patients with moderate liver disease [31%] initiated anti-viral treatment and 23 patients [35%] were still awaiting treatment on 31st October 2001; treatment was contraindicated in 4 patients, withheld in 7 patients, declined by 4 patients and 6 patients were lost to follow-up. 2 patients with cirrhosis initiated anti-viral treatment and 1 patient was awaiting treatment on 31st October 2001; treatment was contraindicated in 4 patients, withheld in 1 patient and 2 patients were lost to follow-up. The median time from liver biopsy to non-trial treatment was 5 months (range 1 to 40 months). The median length of wait in those patients still awaiting anti-viral therapy was 21 months (range 9 to 51 months).

Conclusions: Of the 113 patients who underwent liver biopsy during the study period 66 (58%) would be considered eligible for treatment with combination therapy according to current NICE guidelines. Although 46 of these patients were offered treatment only 22 had started by the end of the follow-up period. Lack of funding was the principal explanation for delay to treatment. Proposed government support to implement NICE guidelines should reduce this delay.

434 THE COMBINATION OF PEGYLATED INTERFERON (PEG-IFN) AND RIBAVIRIN (RIBA) IN THE TREATMENT OF CHRONIC HEPATITIS C (HCV) INFECTION: PRELIMINARY REPORT OF A SINGLE CENTRE EXPERIENCE

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Background: The HCV prevalence in the United Kingdom may be as high as 1%. Patients with chronic HCV infection have been treated with antiviral therapy at the QE Liver Unit. Since September 2000, antiviral treatment comprised pegylated interferon (PEG-IFN, 1–1.5 µg/kg weekly) and ribavirin (RIBA, 1–2 g/day). Treatment was intended for 6 months (non genotype 1 and non-cirrhotic patients) or 12 months.

Patients: At present, 79 patients [median age 44; male 56; non-cirrhotic, 13 cirrhotic] had commenced treatment. Genotype distribution was type 1, 38 type 2 /3, 2 type 4, 5 type 1, 5 type 6. Median pretreatment titre was 6.7x10⁶ copies/ml.

Results: 14 patients were withdrawn from therapy after a median of 16.5 weeks. Indications were: intolerance of symptoms [7], neutropenia [3], psoriasis [1], unstable angina [1], HBV co-infection[1] and mortality.

Abstract 432

<table>
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<tr>
<th></th>
<th>CS</th>
<th>AB</th>
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<th>Overall 30-day Mortality</th>
<th>Liver-related 30-day Mortality</th>
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<td>GI</td>
<td>13</td>
<td>29</td>
<td>32</td>
<td>(28%)</td>
<td>(63%)</td>
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<tr>
<td>GM</td>
<td>2</td>
<td>11</td>
<td>15</td>
<td>(6%)</td>
<td>(33%)</td>
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</table>

*p<0.05, *p<0.001: GI vs. GM

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thyrtoxicosis [1]. At time of analysis 53, 35 and 3 patients completed 3, 6 and 12 months of treatment respectively. Biochemical response (normal AL) was observed for 32/48 at 3 months and 21/32 patients at 6 months. Of those completing 6 months treatment, HCV RNA negativity was achieved for 22/24 (92%), including 4 cirrhotics with genotype 1 (n=1), 2 (n=1) and 3 (n=2). 25 patients required reduction of PEG-IFN and 16 of 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: Combination treatment with PEG-IFN and RIBA achieved biochemical response and early virological clearance for a majority of treated patients. However, side effects may be frequent and severe, and dose reduction of PEG-IFN and/or RIBA is often required.

E118 EVOLUTION OF HEPATITIS B VIRUS DURING PRIMARY INFECTION

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To study HBV evolution in vivo, we evaluated over 1MB-pairs of genetic sequences from PCR-clones obtained prospectively in six patients with acute resolving hepatitis and four patients who progressed to chronic infection. We analysed two genetic loci (3 ORFs: core, surface, and polymerase). 93 mutations were observed, consistent with a relatively stable genetic population throughout infection. The majority of mutations were non-synonymous (average for all regions 81%). Patients with acute resolving hepatitis had a similar frequency of non-synonymous mutations within the core (2 x 10^-4/codon) but a higher frequency of surface/polymerase mutations (1.8 x 10^-4/codon) when compared to the chronic group (1.5 x 10^-4/codon and 0.65 x 10^-4/codon, respectively; p=0.01). Genetic diversity was quantified by the mean Hamming distances (Hd) and the number of strains (Ns) present within a serum sample. Overall, the core region had the greatest genetic diversity when compared to the surface or polymerase regions. A rapid expansion in Hd and Ns occurred in the core region between the earliest time during acute infection and the peak viral load and then a subsequent contraction in genetic diversity occurred as viral load declined. Patients with acute resolving HBV consistently exhibited a higher genetic diversity in all three genetic loci and an increased mutation frequency in surface/polymerase region compared to chronic infection. We speculate that these emerging variants contribute to the evolution of increased virulence, as indicated by a rise in serum LFT's, due to the increased immunological burden they present to the host.

E119 ALBUMIN DIALYSIS (MARS DEVICE) RELIEVES CHOLESTATIC PRURITUS IN A DRAMATIC BUT NON-SUSTAINED MANNER

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Background: Intractable pruritus, a debilitating symptom related to intrahepatic cholestasis, can seriously impair quality of life. The efficacy and tolerability of presently available remedies is limited and unpredictable. Case reports have shown that plasmapheresis, and charcoal haemoperfusion are of some benefit. Molecular Adsorbent Recirculating System (MARS) is a novel dialysis technology which efficiently removes albumin bound substances (including bile salts), with acceptable side effects and low mortality rate. However, there is no definitive proof that MARS is of benefit in relieving pruritus. We conducted a randomised double blind placebo controlled study in patients with intrahepatic cholestasis refractory to standard treatments to determine if MARS is able to significantly improve pruritus.

Patients and Methods: Five patients (2M:3F) with intractable pruritus were studied. The underlying conditions were PSC, chronic rejection, PBC, TPN-cholestasis and drug induced cholestasis in a donor liver, respectively. All patients had received standard and second-line anti-pruritic medication without symptomatic relief. Quality of Life Scores (QOL) scores [SF-12] and pruritus scores were calculated in each patient before and after MARS treatment. The four patients underwent a median of 24 hours (range 16–48 hrs) of albumin dialysis over a 2 to 45 day period.

Results: Pruritus resolved completely in 4/5 patients. QOL scores improved in 4/5 patients at the end of MARS treatment. Pruritus recurred in three patients at a median of 10 days (range 2–28 d). No direct relationship between changes in serum bilirubin and the interval 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.

Conclusions: 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.

E120 ABNORMAL VASCULAR FUNCTION IN HEREDITARY HAEMOCHROMATOSIS: INVESTIGATING THE “IRON HYPOTHESIS”

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Background: Iron excess has been linked with development of coronary heart 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 waveform and deriving the central aortic pressure. Augmentation of this pressure thus provides a measurement of the compliance of the vascular tree, which can be expressed quantitatively as the augmentation index (AIx).

Methods: The AIx of 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.

E121 THE IMPACT OF PORTAL HYPERTENSION IN PRIMARY BILIARY CIRRHOSIS (PBC)

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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 transplant was significantly worse in patients developing PHT (Kaplan-Meier analysis (KMA) p<0.001; 5 year survival (5ys) 68% v 87% for patients free of PHT at the study point). PHT development was not acting simply as a surrogate marker for development of histologically advanced disease as PHT retained its adverse prognostic value when analysis was restricted to patients with histologically advanced disease (Scheuer stage III/IV; KMA p<0.001; 5 ys 66% for stage III/IV disease with PHT v 81% for stage III/IV disease without PHT). Survival was significantly worse in PHT patients developing OV than in non-OV PHT patients (KMA p<0.001; 5ys 63% v 75%). In fact, stage III/IV disease patients with PHT but not OV had similar survival to stage III/IV patients not developing PHT. The adverse outcome associated with OV development did not result simply from the consequences of variceal bleeding as survival following PBC diagnosis was the same in patients developing OV with and without bleeding on follow-up (KMA p=ns; 5ys following PBC diagnosis 62% v 63%, 5ys following diagnosis of varices 25% v25%).
439 NO ASSOCIATION BETWEEN NOD2 POLYMORPHISMS AND SUSCEPTIBILITY TO, OR PROGRESSION OF, PRIMARY SCLEROSING CHOLANGITIS

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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 obliterative 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 SSP-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.

440 PEAK PROPORTION AREA CHANGE (PPAC): A NOVEL METHOD OF THRESHOLD DETERMINATION FOR DIGITAL IMAGE FIBROSIS AREA ESTIMATION ON LIVER BIOPSYS

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Introduction: Digital image analysis allows quantitative assessment of fibrosis on liver biopsy. Accurate determination of a threshold grey-scale level representing fibrous tissue is critical. We present and describe a novel and objective method of determining threshold and compare it with the standard interactive method.

Methods: Digital images of 18 patients with cirrhosis were captured by microscopy and converted to greyscale. Pixel counts at 256 grey levels were measured. Differences between each grey level and fibrosis were calculated and corrected for the number of pixels remaining. Grey level corresponding to maximum change in pixel count was chosen as threshold at which fibrosis area was calculated. Reproducibility was tested in comparison with interactive thresholding by repeating the process 4 times with 30 biopsies for each method.

Results: For the PPAC method correlations of R>0.7, p<0.001 were obtained between each repeated measurement, no significant difference was observed with repeated measures ANOVA (p=0.73), intra-class correlation co-efficient 0.96. For interactive thresholding results were less impressive with correlations (R=0.19-0.64) not all reaching significance, repeated measures ANOVA (p=0.076), intra-class correlation co-efficient 0.77.

Conclusions: The Peak Proportion area change (PPAC) method, described here, for determining threshold in image analysis is objective, reproducible and superior to standard interactive thresholding.

441 ABNORMAL LIVER FUNCTION TESTS FOLLOWING BONE MARROW TRANSPLANTATION: WHAT IS THE AETIOLOGY AND THE ROLE OF LIVER BIOPSY?

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Introduction: Liver dysfunction is common in bone marrow transplant (BMT) recipients. Common 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% autologous 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 autologous 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.

Abstract 441 Table showing cause of deranged LFTs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Iron XS</th>
<th>GVHD</th>
<th>Sepsis</th>
<th>VOD</th>
<th>Others</th>
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<tbody>
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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 mostly 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.
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442 POSTER WITHDRAWN.

443 OESOPHAGEAL CANCER MANAGEMENT: GOOD ENOUGH GUIDELINES?

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 PAS 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 anaemia, 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 25/44 (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 was 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 REFLUX (GORD)
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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 category and gastro-oesophageal reflux.

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 2 (least deprived) 20% (14) had Barrett’s oesophagus and 79% (27%) had 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 consumpion [units per 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. 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=0.01). 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 REFLUX
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 pHRE 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 IEIRE occurred where IEI values dropped by 50% from the baseline (>2 secs).

Results: Overall pHRE had an associated IEIRE on 310/538 (57.6%) occasions. IEIRE were definitively acid (associated pHRE in 310/505 [61%] and non-acid in 105/505 [21%]). Gas RE were detectable using IEI. See 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 pHRE, 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.

Abstract 445

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Total Monitored Reflux Episodes (RE)</th>
<th>pHRE</th>
<th>IEI-RE</th>
<th>Man-RE</th>
<th>Gas RE</th>
<th>Non-acid RE</th>
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<td>140</td>
<td>130</td>
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<tr>
<td>H2RA</td>
<td>538</td>
<td>310</td>
<td>52</td>
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</table>

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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 compared with more palliative 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.
Results: 69 men and 31 women underwent SEMS placement; ages ranged from 40 to 96 years and 61 patients were above 70 years. Tumours were predominantly distal; 67 in the lower third or at the gastro-oesophageal junction. 65 were adenocarcinomas. 88 Ultraflex and 12 Flamingo stents were placed, 50 straddled the gastro-oesophageal junction (GOJ). One patient died immediately following stent placement; 4 further patients died within the first week and 66 within 6 months. Stent migration occurred in 2, tumour overgrowth in 4 and, despite dietary advice, food bolus obstruction in 23. 74 patients were able to take a normal “stent” diet, 13 a blended diet, 7 liquids only and 4 took little because of their poor general condition. Pain was reported in 19 before and 53 following SEMS placement. Regurgitation and vomiting were reported by 37 patients following SEMS. Relief of dysphagia, post stent pain and survival appeared independent of stent position. Vomiting, however, was seen more often when the stent straddled the strictures (48%) than when in the lower oesophageal but not across the junction (36%) and least when in the mid oesophagus (16%).

Conclusions: SEMS provide reasonable relief of dysphagia in most patients with malignant oesophageal disease. However, post SEMS pain is common and often severe and vomiting is frequent when the stent is placed in the lower oesophagus particularly when it straddles the GOJ.

Barrett’s Oesophagus on the Internet: a Misperception 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 primarily concerned with oesophageal cancer. 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 options as well as with an interest in Barrett’s Oesophagus, 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 for 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/compromise or lost to follow-up. This 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 every year as more 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.

Expression of Carbonic Anhydrase Iso-Enzymes in Gastro-Oesophageal and Laryngopharyngeal Reflux Diseases
N. Johnston1, P.E. Ross1, P.W. Dettmar2, M. Panetti3, J.A. Koufman3

Background: Gastro-oesophageal reflux disease (GORD) is a 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 aerodigestive 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-, that could provide an important buffering mechanism in the oesophageal mucosa.

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.

Conclusion: The findings in patients with GORD suggest that expression of CA enzymes is modified and may be an important protective mechanism as it may increase the buffering capacity within the cells. The laryngeal mucosa does not show the same pattern of response, furthermore loss of expression of the CA III iso-enzyme may increase the sensitivity of this epithelium to damage associated with reflux disease.

Esomeprazole 20 mg Compared with Lansoprazole 15 mg for Maintenance Therapy in Patients with Healed Reflux Oesophagitis
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Aim: This study was conducted to compare the standard maintenance dose of esomeprazole 20mg once 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 multicentre trial. During the initial, healing phase of the study, all patients received 4–8 weeks’ open treatment with esomeprazole 40mg. 1236 healed (identified by endoscopy at 4 months of treatment by the GOJ).

ESEMPRAZOLE 20 MG COMPARED WITH LansOPRAZOLE 15 MG FOR MAINTENANCE THERAPY IN PATIENTS WITH HEALED REFUX OESOPHAGITIS

Abstract 452

<table>
<thead>
<tr>
<th>Tooth wear (mean (sd)) and regurgitation</th>
<th>Regurgitation</th>
<th>No regurgitation</th>
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<tr>
<td>Tooth wear</td>
<td>1.52% (5.9%)</td>
<td>0.65% (1.63%)</td>
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<tr>
<td>Salivary flow rate (median (range)) and hoarseness</td>
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<tr>
<td>Hoarseness</td>
<td>0.66 ml/min (0.4–1.1)</td>
<td>1.6 ml/min (1.1–2.6)</td>
</tr>
<tr>
<td>No hoarseness</td>
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</table>

P = 0.048

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 = 0.03, 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.

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-dependent 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.

452 TOOTH WEAR, SALIVA AND SYMPTOMS OF GORD: IS THERE A RELATIONSHIP?

R. Moazzez1, A. Anggiansah2, D. Bartlett1, A. Chandra2, W.J. Owen1.
1Department of Surgery and 2Division of Conservative Dentistry, GKT School of Medicine, UK

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 GORD were evaluated. Oesophageal pH monitoring was performed, and 24-hour ambulatory pH testing. GORD was defined using the 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 saliva 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.

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 was measured using 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 0°C and 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. 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.

Conclusions: Two conditions is unclear. This study aimed to investigate the relationship between saliva, dental erosion and reflux symptoms.

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PHOTODYNAMIC THERAPY (PDT) FOR BARRETT’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 optimum 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 4 hours, 30 or 60mg/kg ALA at 6 hours, or 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 65mW/cm², with a total fluence of 85J/cm². Endoscopy with quadrantic biopsies 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.

THE PREVALENCE OF BARRETT’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% C.I. 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.

60mg/kg ALA at 6 hours, or 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 65mW/cm², with a total fluence of 85J/cm². Endoscopy with quadrantic biopsies was repeated 4 weeks later.

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 which 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.

TRANSFECION INTO AND EXPRESSION OF P53 IN THE HUMAN OESOPHAGUS: AN EX VIVO STUDY

E. Pohler, P.E. Ross, J.F. Dillon. Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 4HN, UK

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 are 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.

Abstract 455

<table>
<thead>
<tr>
<th>Age bands</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
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<tbody>
<tr>
<td>Males</td>
<td></td>
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<td>Females</td>
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www.gutjnl.com
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^{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^{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^{WAF1} protein was readily detectable in biopsies transfected with the p53 gene, at levels significantly higher than those seen in the controls.

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^{WAF1}, a gene downstream in the pathway to cell cycle arrest. This has therapeutic potential.

458 A 5-YEAR, DOUBLE-BLIND, RANDOMISED COMPARISON OF RABEPRAZOLE AND OMEPRAZOLE IN GORD MAINTENANCE TREATMENT: SERUM GASTRIC RESULTS

B. Thjodleifsson1, N.M. Miller2, J.E. Saller1, K.D. Bardhan3. 1Ninewells Hospital and Medical School, University of Dundee, UK; 2Reckitt Benckiser Healthcare Ltd, Hull, UK

Background: Treatment with proton-pump inhibitors increases serum gastrin levels, but there is little evidence from prospective randomised trials about the effects of long-term treatment.

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 serum gastrin concentrations.

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. Serum gastrin concentrations were measured during the study; treatment effects were investigated in an ANOVA model of the log-transformed area under the gastrin concentration–time curve (AUC).

Results: Mean serum gastrin concentrations are shown in the graph. The data had a highly skewed distribution, particularly in the omeprazole group. The differences among treatments in the AUC were not statistically significant.

Conclusions: Increases in serum gastrin concentrations during long-term rabeprazole or omeprazole treatment were modest in most patients, but were substantial in some patients taking omeprazole.
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 high dose twice 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.

**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 guidance and without the need for fluoroscopy. Microvasive (Boston Scientific) stents were used. The proximal position 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 visualisation 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 visualisation 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.

**462 THE BARRETT’S OESOPHAGUS DATABASE FOR SHEFFIELD (BODS)**

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**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 patient 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.

**463 TOWARDS SELECTIVE MUCOSAL ABLATION FOR BARRETT’S OE SOPHAGUS: STUDIES OF PHOTODYNAMIC THERAPY USING mTHPC IN THE NORMAL RAT COLON**

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**Background:** Oesophagectomy carries a significant risk of major morbidity or mortality. Photodynamic therapy (PDT) shows potential as a minimally-invasive treatment to ablate high-grade dysplasia in Barrett’s oesophagus. The challenge is to completely and selectively remove mucosa, as damage to underlying tissue may result in oesophageal stenosis. Meso-tetrahydroxyphenylchlorin (mTHPC - QuantumNova) is a potent photosensitiser used for oesophageal PDT. With the standard regime, mTHPC may induce oesophageal muscle injury. Variation of treatment parameters may allow enhancement of mucosal selectivity.

**Methods:** Fluorescence studies in Wistar rats given mTHPC (0.1mg/kg) intravenously were killed at intervals. Frozen sections of colon were examined by fluorescence microscopy and the level of fluorescence quantified in the mucosa and muscle layers. PDT studies - Intravenous mTHPC (0.1, 0.05 or 0.025mg/kg) was administered. After an interval (drug-light interval) of 4, 24 hours or 4 days, normal colon was treated at laparotomy using a diffuser fibre and 652nm light. The light dose was 3, 9 or 27J at a power of 10, 30 or 100mW. After three days the extent of mucosal and muscle necrosis was graded histologically and a selectivity ratio derived (mucosal over muscle score).

**Results:** Fluorescence in colonic mucosa peaked at 24 hours while muscle fluorescence rose until 5 days. Mucosal selectivity was greatest at 24 hours suggesting this was the optimum time for PDT. Histologically, after PDT some mucosal necrosis was seen in all animals. This was greater at 24 hours than other times (p<0.04). PDT at low power caused significantly more mucosal and muscle necrosis than at high power but selectivity ratio was not significantly better (p<0.09). Selectivity was not improved by lowering drug dose (p=0.07).

**Conclusions:** Mucosal selectivity was best achieved in this model using a 24-hour drug light interval. Further work is needed to determine the optimum parameters for clinical use.

**464 LAMININS: DISTRIBUTION IN NORMAL UPPER GUT TRACT AND BARRETT’S OESOPHAGUS**

U. Dave, M.M. Walker, H. Ebrahim, E. Townsend, M. Burke, M.R. Thurstz. Faculty of Medicine and Histopathology, Imperial College, St Mary’s Campus, Harefield Hospital, UK

Barrett’s oesophagus is a metaplastic change in the epithelium that is strongly associated with oesophageal cancer. Laminin, a component of the epithelial basement membrane, plays an important role in the regulation of cellular differentiation. There is limited information on the distribution of laminin chains in the upper gastrointestinal tract. Furthermore, the antibodies used in earlier studies have been ascribed incorrect specificity. The distribution of laminin chains in Barrett’s oesophagus has not been previously described.

**Method:** The distribution of laminin isoforms was documented in the normal upper gastrointestinal tract and in Barrett’s oesophagus from endoscopic biopsies and surgical oesophagectomy specimens. Immunohistochemistry was performed on frozen sections using the following primary antibodies (antigen indicated in brackets): BM2 (α3 chain), S45 (β1), S5F11 (β2), 6F12 (β3), B8B11 (β2), MAb1920 (β1), MAb1922 (α2), MAb1924 (α3), MAb2041 (β1), MAb19562 (β2) MAb EB7 (α1).

**Results:** The α1 laminin chain is expressed in submucosal glands and duct basement membranes in squamous oesophagus and Brunner’s glands in the duodenum but is not expressed in Barrett’s oesophagus or elsewhere in the upper GI tract. The α2 chain is expressed in the cytoplasm of the basal cells in surface epithelium and basement membrane of the glandular epithelium. The β2 laminin chain is present in a continuous fashion in squamous epithelial basement membrane but in Barrett’s epithelium, cardiac, gastric body and duodenum it is discontinuous and not expressed at the surface and only expressed in the glandular basement membrane. Constituents of laminin 5 (α3, β3, γ2 chains) are expressed in a continuous fashion in squamous epithelial basement membrane but in cardiac, gastric body and duodenum and Barrett’s oesophagus are expressed in surface epithelial basement membrane with a sharp decline in glandular and gastric pit basement membranes.

**Discussion:** The site specific distribution of α1and β2 laminin chains may have an important role in Barrett’s metaplasia in the oesophagus.
Hypomagnesaemia due to malabsorption is not always responsive to oral magnesium oxide supplementation alone

We read with interest the Gut File report by Dr Ross and colleagues of hypomagnesaemia due to malabsorption, eventually responding to oral magnesium oxide supplementation (Gut 2001;48:857–8). Our experience however has been different. For the past seven years we have managed a 65 year old woman with short bowel syndrome (right hemicolectomy for Duke's C colorectal carcinoma and thereafter a terminal ileal resection for abscess formation).

High ileostomy output was initially difficult to manage (after excluding infection, secretory gut hormone tumours by normal hormone levels, and despite dietary and pharmacological modifications). Clinical signs of hypomagnesaemia and hypocalcaemia ensued. An initial trial with magnesium glycerophosphate (September 1992 to December 1993) was insufficient to sustain her serum magnesium levels requiring frequent “top ups” of intravenous magnesium. In December 1993, she was switched to magnesium oxide supplementation but despite this the frequency of intravenous magnesium “top ups” were not reduced. Compliance was not deemed to be an issue with our patient.

Since then we have managed this woman while still taking magnesium oxide supplements with almost 3–6 monthly “top ups” were not reduced. Compliance was not deemed to be an issue with our patient.

We refer not be sufficient, especially in patients with extensive resection of the small bowel, as demonstrated in our patient.

References

Regulation of gastric function by gastrin releasing peptide

Hildebrand et al reported data suggesting that gastrin releasing peptide (GRP) may be a physiological regulator of pre- and postprandial gastric acid secretion (Gut 2001;49:23–8). Interestingly, these effects were independent of gastrin and the authors appropriately questioned the physiological role of gastrin in regulating gastric secretion. Several aspects of the authors’ conclusions deserve further clarification and discussion.

The authors concluded that alteration of somatostatin secretion is unlikely to explain the acid inhibitory action of BIM26226 because the GRP antagonist did not alter somatostatin mRNA levels. They also argued that the lack of change of gastrin mRNA supported the physiological data showing no alteration in gastric secretion by BIM26226. In short term experiments such as these, it is incorrect to assume mRNA levels reflect peptide secretion rates. In longer term studies this may be true, but it is clear that peptide synthesis, translation, synthesis, and secretion are all regulated independently and changes may not occur in parallel. Indeed, previous studies with GRP infusion in humans have shown that although secretion of gastrin peptide was enhanced, gastrin mRNA levels were actually decreased. Thus it would be unwise to exclude the possibility of any peptide having a role in this dynamic system on the basis of unchanged mRNA levels.

The authors also state that muscarinic receptor activation inhibits somatostatin secretion from D cells. This is correct for fundic but incorrect for antral D cells. Muscarinic activation actually stimulates somatostatin release from antral D cells. This would be more compatible with the mechanisms suggested by the authors: GRP enhanced neural acetylcholine release and this reduced fundic somatostatin mediated inhibition of histamine and acid secretion; in the antrum, stimulation of somatostatin release would then impair the gastrin response and contribute to the lack of gastrin response seen in the current experiments.

The authors felt that previous in vitro studies of G cells were difficult to assess but they appear to have overlooked detailed studies of cultured human G cells. Squires et al demonstrated two receptors of the GRP family in antral tissue, namely GRPR (BB1) and BRS-3 (BB3). BRS-3 is an orphan receptor that does not functionally respond to bombesin/GRP except at very high concentrations. Single cell microfluorometry clearly showed antral G cells responding to bombesin/GRP except at very high concentrations. Further studies with BIM26226 under different conditions, to more fully describe the pathophysiological role of GRP, are awaited with interest.

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References

Authors’ reply
We appreciate Dr Beales’s interest in our study describing the effects of gastrin releasing peptide (GRP) and its antagonist BIM26226 on gastrin acid secretion in healthy male subjects. We described the effects of endogenous GRP on acid output were independent of plasma gastrin in humans. These results are clearly in contrast with findings in animals and suggest species differences. Thus the molecular mechanism of GRP stimulated acid secretion as the effects of endogenous GRP on acid output were independent of plasma gastrin in humans. These results are clearly in contrast with findings in animals and suggest species differences. Thus the molecular mechanism of GRP stimulated acid production has not directly been substantiated in humans. This is not likely to be investigated in the near future because the antagonist BIM26226 is no longer available for human use.

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Correspondence to: Professor C Beglinger, beglinger@chr.ch

Osteoporosis is not a specific complication of primary biliary cirrhosis (PBC)
Newton et al (Gut 2001;49:282–7) described a retrospective study on bone mineral density (BMD) in a large cohort of patients with primary biliary cirrhosis (PBC). The authors concluded that osteoporosis is not a specific complication of PBC, but certain weaknesses in the study design do not support this conclusion.
(A) The authors did not include age and sex matched controls from the general population, or control groups with different types of liver disease.
(B) A proper methodological design comparing osteoporosis in PBC and in a normal population should calculate the standardised incidence ratio of osteoporosis for the two cohorts by comparing the observed incidence versus the expected incidence. The calculation should include 95% confidence intervals according to exact Poisson limits. This is not likely to be revisited the perceived dogma that patients with primary biliary cirrhosis (PBC) are predisposed to osteoporosis. It was pleasant to note that our findings compare favourably with work from her group. We would also like to take this opportunity to draw attention to two further studies which have been presented in abstract form since the submission of our manuscript, which confirm that there is no increase in prevalence of osteoporosis and no increase in fracture rate in PBC patients compared with appropriately matched normal controls. A further study has also been published recently describing bone mineral density in a selected series of patients with PBC in whom the proportion with osteoporosis (defined by T score) was comparable with that seen in our series. We were pleased to note that in this prospective series other risk factors for osteoporosis were examined. They concur with our finding that increased age is an independent risk factor, although they do not present mean Z score data (bone mineral density data controlled for both sex and age). Their group, we would argue, was younger and had more severe disease than patients in our series, whom we would regard as more representative of the whole PBC population.

We were pleased to note that in this prospective series other risk factors for osteoporosis were examined. They concur with our finding that increased age is an independent risk factor, although they do not present mean Z score data (bone mineral density data controlled for both sex and age). Their group, we would argue, was younger and had more severe disease than patients in our series, whom we would regard as more representative of the whole PBC population.

In our study we demonstrated that although 85/272 (31%) patients had osteoporosis, as defined by the WHO (T score) at the time of their first DEXA scan, mean Z score at the neck of femur was –0.1 and at the lumbar spine 0.1. As Z scores represent bone mineral density compared with an age and sex matched population, this suggests that the prevalence of osteoporosis seen in PBC is a reflection of the fact that this is predominantly a disease of postmenopausal women who show a generalised increased prevalence of osteoporosis. The use of Z scores implicitly controls our data for age and sex norms. We agree with Professor Floreani that readdressing the question of osteoporosis prevalence in other chronic liver diseases (both cholestatic and non-cholestatic) would be of interest but we feel that this is not relevant to the current study.

Given the very real problems experienced by some PBC patients as a result of osteoporotic fracture (particularly in the early post-transplant period), further study of the aetiology is appropriate (although the retrospective nature of the current study makes the suggested logistic regression analysis inappropriate). The message that we (and more recently others) have been communicating is that the search for risk factors for osteoporosis should not be focused on liver disease specific factors but could more usefully be directed at more generalised population risk factors.

Table 1 Risk factors for osteoporosis in liver diseases

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<tr>
<th>Common risk factors</th>
<th>Cholestatic related risk factors</th>
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<tr>
<td>• Cirrhosis</td>
<td>• Calcium malabsorption</td>
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<tr>
<td>• Female sex</td>
<td>• Vit D malabsorption</td>
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<tr>
<td>• Old age</td>
<td>• Hypothalamic ischaemia</td>
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<tr>
<td>• Alcohol consumption</td>
<td>• Cholestyramide therapy</td>
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<td>• Hypogonadism</td>
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<td>• Steroid therapy</td>
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<tr>
<td>• Low BMI</td>
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<tr>
<td>• VDR polymorphism</td>
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<tr>
<td>• Impaired conversion to 25-OH Vit D</td>
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<td>• Reduced osteocalcin activity</td>
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BMD, body mass index; VDR, vitamin D receptor

Authors’ reply
We read with interest the letter of Professor Floreani in which she agrees that it is timely to revisit the perceived dogma that patients with primary biliary cirrhosis (PBC) are...
Expression of isoforms of nitric oxide synthase in collagenous colitis

We read with interest the study by Perner et al (Gut 2001;49:587–94) investigating expression of various isoforms of nitric oxide synthase (iNOS, eNOS, and nNOS) in non-inflamed colon, collagenous colitis, and ulcerative colitis. Inducible NOS (iNOS) was identified by immunohistochemical analysis in the epithelium of patients with non-inflamed colon. The authors concluded that this might be a result of bowel preparation with bisacodyl.

Increased synthesis of nitric oxide has been detected by a number of different methods in patients with ulcerative colitis.1,2 We have previously found that physiological expression of iNOS in histologically normal colon using reverse transcription-polymerase chain reaction (RT-PCR), immunohistochemistry, and immunoblotting3. Tissue from three different sources was studied. Surgical specimens were obtained from patients undergoing colectomy for colorectal cancer who had undergone bowel preparation with sodium picosulphate, colonic mucosal biopsies from patients who had received no bowel preparation. This last group of patients also underwent colonoscopy with sodium picosulphate preparation confirming the absence of colonic pathology. iNOS mRNA was identified in all samples by RT-PCR. iNOS protein was detected by immunoblotting in 77% of samples, by immunostaining in 80% of surgical specimens, and in 90% of biopsy specimens.4 It is therefore possible that expression of iNOS in epithelial cells reported by Perner et al is, as we found, a result of physiological expression of iNOS rather than a secondary phenomenon as a result of bisacodyl bowel preparation.

The reason for iNOS expression in normal colonic epithelium is not currently clear. Nitric oxide production may aid maintenance of the epithelial barrier by preventing bacterial translocation or by inducing apoptosis. It is also possible that its presence represents a link between dietary or other luminal factors and the development of colorectal cancer.

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References

Authors’ reply
We thank Cameron et al for their comment on our recent publication and important observations that suggest physiological expression of inducible nitric oxide synthase (iNOS) in histologically normal human colon. As we observed subtle iNOS labelling in colonic mucosal biopsies from our group of controls with non-inflamed bowel, we have subsequently studied whether bowel preparation with bisacodyl or polyethylene glycol prior to sigmoidoscopy might induce iNOS expression.

Ten healthy non-smoking male subjects were investigated. Mucosal biopsies were taken from the sigmoid colon prior to bowel preparation and again 12 hours after rectal administration of an enema consisting of bisacodyl (100 mg) or polyethylene glycol 3000 (6.4 g in 100 ml of water) in randomised order. Expression of iNOS protein was quantified by western blot analysis and localised by immunohistochemistry.

iNOS was expressed in the colonic mucosal biopsies from all subjects and localised in epithelial cells, particularly at the luminal border of the epithelial cells and more pronounced in the crypt epithelium. Expression of iNOS was unaffected by bowel preparation with bisacodyl or polyethylene glycol (fig 1). Hence we agree with Cameron et al that expression of iNOS in epithelial cells is possibly a result of physiological expression of iNOS rather than a secondary phenomenon as a result of the bowel preparation per se or the effect of the secretagogue laxative bisacodyl. For the reasons given above, we also agree that nitric oxide may be important in maintaining the epithelial barrier and may represent a link between dietary or other luminal factors and the development of colorectal cancer, as hypothesised by Cameron et al, although high iNOS expression in collagenous colitis is not associated with an increased risk of malignancy.

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NOTICES

Gastroenterology and Endotherapy European Workshop: XXth Anniversary
This course will be held on 17–19 June 2002 in Brussels, Belgium. Further information: Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels, Belgium. Tel: +32 (0)2 055 49 00; fax: +32 (0)2 555 4901; email: info@broadmedical.org; website: www.broadmedical.org

EASL Monothematic Conference on Vascular Function in Liver Disease
This conference will take place on 30 June to 2 July 2002 in London, UK. Further information: Professor Jordi Bruix, EASL Liaison Bureau, c/o Kennes International, 17 rue du

Figure 1 Expression of inducible nitric oxide synthase in mucosal biopsies from the unprepared (Unprep) sigmoid colon and 12 hours following bowel preparation with bisacodyl (Bis) or polyethylene glycol 3000 (PEG), analysed by western blotting and quantified by densitometry relative to a reference. Values in individual subjects are represented by circles and connected by lines. OD, optical density.
Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0488; fax: +41 22 732 2850; email: info@easl.ch; www.easl.com. Deadline for abstract submission 15 May 2002. Further information: kmoore@rfc.ucl.ac.uk; tel: +44 (0)207 433 2876.

5th International Workshop on Pathogenesis and Host Response in Helicobacter Infections
This will be held on 4–7 July 2002 in Helsingør, Denmark. Further information: Dr Tina Ken Hansen, Department of Cardiology-Endocrinology E, Frederiksberg Hospital, Ndr. Fasanvej, DK-2000 Frederiksberg, Denmark. Fax: +45 3545 7708; email: helpati@biobase.dk

ESPEN 2002
The European Society for Parenteral and Enteral Nutrition will be hosting its annual meeting on 31 August to 4 September 2002 in Glasgow, UK. The organisers anticipate 300 delegates, principally from Europe but also from the USA and the Far East. Further information: Mrs Pat Howard, Honorary Secretary, BAPEN, Head of Nutrition and Dietetic Services, Bristol Royal Infirmary, Bristol BS2 8HW, Tel: +44 (0)117 928 2049; Fax +44 (0)117 928 3005; email: pat.howard@ubht.swest.nhs.uk

Postgraduate Gastroenterology
This course will be held on 15–18 September 2002 in Oxford, UK. The course has been designed for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include: Barrett’s Oesophagus; The Case for Endoscopic Surveillance Debate; Liver Disease; Bacteria and the Gut; IBD Therapeutics, Gastrointestinal Bleeding, Endoscopic Training. Further information: Professor Derek P Jewell, University of Oxford, Nuffield Department of Medicine, Gastroenterology Unit, Gibson Laboratories, 2nd Floor, Radcliffe Infirmary, Block 21, Woodstock Road, Oxford OX2 6HE. Tel: +44 (0)1865 224829; fax: +44 (0)1865 790792; email: derek.jewell@ndm.ox.ac.uk; website: www.medicine.ox.ac.uk/gastro

3rd World Chinese Congress of Digestology
This congress will take place on 23–25 September 2002 in Beijing, China. Further information: Lian-Sheng Ma, President of WCCD, PO Box 2345 Beijing 100230, China. Fax: +86 6589 1893; email: wcjd@public.bta.net.cn