Neurogastroenterology/
Motility free papers 001–011

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

S.D. Parry, J.R. Barton, M.R. Welfare. Northumbria Division, University of Newcastle Faculty of Medicine, North Tyneside Hospital, Rake Lane, North Shields NE29 8NH, UK

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.

002 GENETIC INFLUENCES IN IRITABLE BOWEL SYNDROME: A TWIN STUDY

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

Methods: 4480 unselected twin pairs from a national volunteer twin register were asked to complete a validated questionnaire. IBS genes shared) and dizygotic (DZ) (approximately 50% of genes have therefore studied IBS symptoms in monozygotic (MZ) (100% of genes contribution to the visceral hypersensitivity of patients with IBS. We lies of patients with IBS has recently been described. This may be due

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

S. Lal, J. Mclaughlin, M. D’Amato1, G. Giampuelo1, G.J. Dockray2, A. Varro2, D.G. Thompson. Hope Hospital, Salford; 1Rotta Research Laboratory, Monza, Italy; 2Physiology Laboratory, Liverpool University, UK

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 Dexlroxiglumide, 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. dexlroxiglumide (Dex; 5–15 mg/kg/h) or saline (Sol) and either intragastric vehicle (Veh) or C12 followed by water infusion. Data are mean±SEM (ml) compared by ANOVA followed by post hoc multiple comparison tests as appropriate.

Results: (a) Subjects tolerated more water following vehicle infusion than C10 or C12. There was no significant 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.

Abstract 001

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<td>197</td>
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* p = NS versus DZ twins.

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the volume of gastric contents aspirated at the end of the infusion period following any of the test meals (veh: 104±5±0.12; C10:1071±153; C12:1065±1.47), 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: 1119±210 (C12 vs. other conditions), indicating a CCK-1 receptor mediated effect.

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

GASTRIC MUCOSA IS INNERVATED BY HIGH THRESHOLD ACID SENSING NON-CAPSACIN SENSITIVE SPINAL AFFERENTS
J.I.W. Jones, D.A. Kendall, P.J. Mills, C. J. Hawkey. Division of Gastroenterology, University Hospital, Nottingham NG7 2UH; Biomedical Sciences, University of Nottingham, UK

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 gastric mucosa of 10 Wistar rats 2–4 weeks before removal of their duodenum and dorsal root ganglia (DRG). Cultured DRG cells were placed in a perfusion chamber mounted on a fluorescence microscope where those of gastric origin were identified by excitation of the Texas Red within them. The cells were loaded with the calcium sensitive ionophore, FURA 2-AM to detect the rise in calcium concentration accompanying cell activation and perfused with a HEPES based buffers from pH 7.4 to pH 6.1 to establish thresholds for cell activation. Following this, cells insensitive to pH 6.1 but sensitive to pH 5 were identified and the effects of exposure to the vanilloid receptor antagonist Capsazepine (5µM) and agonist 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 7.4). Following this, pH 6.1 and pH 5 were chosen as low and high threshold stimuli respectively. 126 cells of gastric (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 identified by excitation of the Texas Red within them. The cells were loaded with the calcium sensitive ionophore, FURA 2-AM to detect the rise in calcium concentration accompanying cell activation and perfused with a HEPES based buffers from pH 7.4 to pH 6.1 to establish thresholds for cell activation. Following this, cells insensitive to pH 6.1 but sensitive to pH 5 were identified and the effects of exposure to the vanilloid receptor antagonist Capsazepine (5µM) and agonist Capsaicin (5µM ) were studied.

Conclusion: The gastric mucosa is innervated by high threshold non-capsacin sensitive neurons. These cells may be important in sensing acidification of the mucosa in response to injury, probably through non-capsaicin sensitive neurons. These cells may be important in sensitising acid sensitive spinal nerves to the presence of luminal acid.

5-HT, RECEPTOR AGONISM SUPPRESSES POST-PRANDIAL ANTPYLODUODENAL MOTILITY IN MAN
E.L. Calvert, L.A. Houghton, P.J. Whorwell. Dept of Medicine, University Hospital of South Manchester, Manchester, M20 2LR, UK

5-HT, receptor agonism delays gastric emptying.1,2 This is associated with prolongation of the lag phase1 and relaxation of the gastric fundus.1 The aim of this study was to assess the effect of 5-HT, receptor agonism on post-prandial antpyloro-duodenal motility.

Methods: Antral (3 sites, 1 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, 2 cm apart) or placebo (P) (6mg, 2 cm apart). Treatment order was randomised and double blind.

Results: During the first post-prandial hour 5-HT significantly decreased antral activity [index: 5.27 mmHg (8, 109) mmHg, median (IQR) v placebo 105 mmHg (67, 320) mmHg; p < 0.05], pyloric [13 mmHg (5, 25) mmHg v 63 mmHg (40, 82) mmHg; p < 0.02] and duodenal motility [78 mmHg (40, 203) mmHg v 291 mmHg (143, 458) mmHg; p < 0.05]. During the 2nd post-prandial hour, only pyloric motility was significantly reduced [21 mmHg (8, 38) mmHg v 38 mmHg (21, 62) mmHg; p < 0.02], with neither antral (30 mmHg (15, 199) mmHg v 238 mmHg (231, 365) mmHg) nor duodenal (92 mmHg (55, 207) mmHg v 251 mmHg (120, 355) mmHg) motility being significantly affected. By the 3rd hour there were no significant differences in either antral (56 mmHg (11, 230) mmHg v 143 mmHg (11, 338) mmHg), pyloric (18 mmHg (7, 42) mmHg v 12 mmHg (5, 24) mmHg) or duodenal (70 mmHg (57, 101) mmHg v 85 mmHg (46, 113) mmHg) motility between S and placebo groups. Finally the number of isolated pyloric pressure waves2 were not affected by S (1st hour: 77 ± 40, 90 ± 68; 50, 94, 2nd hour: 53 ± 18, 168) v 40 ± 27, 63; 3rd hour: 36 ± 8, 64 v 18 ± 3, 50).

Conclusion: 5-HT, receptor agonism with S suppresses antpyloro-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.


5-HT, RECEPTOR AGONISM DELAYS GASTRIC EMPTYING.
S.J. Dunlop, D. Jenkins, R.C. Spiller. Divisions of Gastroenterology and Chemical Pathology, University of Leicester; Dept of Chemical Pathology, University of Leicester, “Glaxo Wellcome, Stockley Park, UK

Meal ingestion is often associated with an exacerbation of gastrointestinal symptoms in patients with IBS.1 Furthermore, plasma 5-HT concentrations appear to increase more after a meal in patients with diarrhoea predominant IBS than healthy volunteers,2 suggesting that abnormalities in 5-HT release may be responsible for the postprandial symptoms associated with IBS. We have assessed platelet depleteted plasma 5-HT concentration for 2 hours (60 minute intervals) under fasting conditions, and then for a further 4 hours (at 30 minute intervals) after a standard carbohydrate meal (457 kcal) in 21 female patients with diarrhoea predominant IBS (aged 19–50 yrs). IBS symptomatology, in particular abdominal pain and urgency, was assessed throughout the study, and platelet depleteted 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 platelet depleteted 5-HT concentration than patients without any symptoms (postprandial area under the curve (AUC) v fasting AUC) with symptoms: 223 (adjusted geometric mean) v 311 mmHg (55, 207) mmHg; p=0.033). Furthermore, the peak postprandial concentration of 5-HT was significantly higher in patients “with” compared with those “without” postprandial exacerbation of their IBS symptomatology (peak: with symptoms, 18.5 ± 19.3/mg/ml v without symptoms, 8.7 mg/ml; ratio with/without symptoms, 2.13 ± 0.94; 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.


CORRELATION OF 5-HT-CONTAINING ENTEROENDOCRINE CELL NUMBERS WITH MUCOSAL LYMPHOCYTES IN NORMAL RECTAL MUCOSA
S.P. Dunlop, D. Jenkins, R.C. Spiller. Divisions of Gastroenterology and Pathology, University Hospital, Nottingham, UK

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

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

Methods: Twenty young [median 27 yrs (21–33)] and twenty older healthy volunteers [median 50 yrs (45–70)] underwent colonic transit measurement and rectal biopsy. These were immuno-stained using antibodies to the following markers: synaptophysin, 5HT & PY (enteroendocrine cells), CD3 (lymphocytes) and mast cell tryptase (mast cells).

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THE ROLE OF ANTICIPATION IN THE BRAIN PROCESSING OF HUMAN VISCERAL PAIN


Introduction: Psychophysicists 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 and an autonomic response can be produced in the gastrointestinal (GI) tract. We examined whether anticipation of visceral pain can alter the processing of visceral sensory information.

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 silicone balloon attached was passed trans-nasally into the distal oesophagus. Magnetic Resonance Imaging: Non-contiguous axial slices were acquired using a 1.5 Tesla system and an event related design. Results: During the learning phase anterior cingulate cortex, bilateral insula, thalamus, left cerebellum, 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.

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 and economic burden for gastroenterologists. It may often prove difficult to treat 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, such as the Hospital Anxiety and Depression Scale (HAD-A & HAD-D) and a IBS disease specific quality of life tool (IBS-QoL). Measures 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 depression (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.

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

L.M. Gladman, D.A. Gorard. Wycombe Hospital, High Wycombe, Bucks HP11 2TT, UK.

Patients with functional gastrointestinal (GI) disorders in primary care differ from those seen in hospital clinics. General practitioners (GPs) and hospital specialists may have different views of functional disorders.

A questionnaire asking about understanding of functional GI disorders was sent to a random sample of 200 UK GPs, and a random sample of 200 clinician members of the British Society of Gastroenterology (consultants). Non-responders were sent reminders after 1 month. 137 (69%) GPs and 167 (84%) consultants replied. Not all answered all questions. 62 GPs believed functional GI symptoms to represent a “real” currently unexplained GI disorder; 67 believed that the symptoms have a psychosomatic basis, probably somatisation of a psychological illness. One GP believed such symptoms were imaginary. In contrast most, 120, consultants believed functional GI symptoms represent a real GI disorder with 36 perceiving them to have a psychosomatic basis, p = 2.56, p<0.001. However GPs and consultants had similar perceptions about the prevalence of psychological illness in their functional GI patients. A fifth of each group believed psychological disturbance to be present in 15–30% of patients, and the rest believed it to be present in >30% of patients. More consultants believed understanding of functional GI disorders has improved in the last 20 years. 

THE IMPACT OF GUT DIRECTED HYPNOTHERAPY UPON 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 (55 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 (22.5%) and abdominal bloating in 5 (6.5%). Physical symptoms were prospectively recorded using seven day diary cards. Outcome 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 depression (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.

ATTITUDES OF GENERAL PRACTITIONERS AND HOSPITAL SPECIALISTS TO FUNCTIONAL GASTROINTESTINAL DISORDERS

L.M. Gladman, D.A. Gorard. Wycombe Hospital, High Wycombe, Bucks HP11 2TT, UK.

Patients with functional gastrointestinal (GI) disorders in primary care differ from those seen in hospital clinics. General practitioners (GPs) and hospital specialists may have different views of functional disorders.

A questionnaire asking about understanding of functional GI disorders was sent to a random sample of 200 UK GPs, and a random sample of 200 clinician members of the British Society of Gastroenterology (consultants). Non-responders were sent reminders after 1 month. 137 (69%) GPs and 167 (84%) consultants replied. Not all answered all questions. 62 GPs believed functional GI symptoms to represent a “real” currently unexplained GI disorder; 67 believed that the symptoms have a psychosomatic basis, probably somatisation of a psychological illness. One GP believed such symptoms were imaginary. In contrast most, 120, consultants believed functional GI symptoms represent a real GI disorder with 36 perceiving them to have a psychosomatic basis, p = 2.56, p<0.001. However GPs and consultants had similar perceptions about the prevalence of psychological illness in their functional GI patients. A fifth of each group believed psychological disturbance to be present in 15–30% of patients, and the rest believed it to be present in >30% of patients. More consultants believed understanding of functional GI disorders has improved in the last 20 years.
Oesophageal free papers

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

Z.H. Khan1, E. Simpson1, A.T. Cole1, I. Macdonald1, D. Pye1, A. Austin1, J.G. Freeman1. 1Department of Gastroenterology, Derby City Hospital, Derby, UK; 2University Department of Physiology and Medical Physics, Queens Medical Centre, Nottingham, UK

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

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

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

Results: Ten patients completed the study protocol. The average caloric intake remained the same throughout the study period in all these patients. 9/10 (95% CI 0.60, 0.98) lost weight on diet alone. The mean gain on thalidomide in the following two weeks was 1.75 kg (median 1.33 kg). A similar trend was shown in lean body mass. There were missing data for one patient, so nine were analysed. 8/9 (95% CI 0.57, 0.98) showed weight gain on thalidomide. The mean increase in 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 increase in 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. Amongst hormonal assay, changes in catecholamines and cortisol were measured at the entry and then after two weeks on diet alone. The mean change in thalidomide in the following two weeks was 1.60 kg (95% CI 0.2, 3.31). A similar trend was shown in lean body mass.

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

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

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

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

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

Results: 243 patients entered the study, of whom 123 completed all 3 years of treatment. Relapse rates were 9/78 (11.5%) in the 20 mg rabeprazole group, 8/82 (9.9%) in the 10 mg rabeprazole group, and 11/83 (13.3%) in the 20mg omeprazole group. The differences in relapse rates were not statistically significant. All three treatments were safe and well tolerated.

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

GORD over 5 years of treatment.

Oesophageal Motor Function and pH Studies Change the Management and Outcome of Patients with Non-cardiac Chest Pain

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

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

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

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

Conclusions: A positive diagnosis of oesophageal dysmotility or reflex 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.

Oesophageal Manometry and pH Studies Change the Management and Outcome of Patients with Non-cardiac Chest Pain

Reference: The assessment of patients with NCCP using OM and pH studies was found to be useful in changing the management of patients and altering the diagnosis of NCCP.

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

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

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

Methods: Combined pressure and pH monitoring was undertaken in 10 neonates requiring assisted ventilation using Dentsleeve...
micromanometric assembly and a paediatric (1.5 mm diameter) 
antimony pH sensor. Study repeated when baby was off the ventilator.

**Results:** Mean gestational age = 33 weeks and mean birth weight 1510 grams (range 28–36 weeks). Mean duration of recording = 58 minutes. LOS pressure = 20 mmHg off ventilation and 40.6 mmHg during positive pressure ventilation. A total of 683 pressure wave sequences were recorded. There were 4 major patterns normal peristalsis (69.8%, of which 16.5% low amplitude), reverse peristalsis 3.6%, synchronous activity 3.2%, non transmitted activity 21.7%. Eleven waveforms (1.6%) could not be adequately categorised. Reflux episodes [pH drop > 0.5 for 10 seconds] = 50 with a mean reflux duration of 22 seconds. An average of 2 normal swallows were required to return pH to pre reflux levels.

**Conclusion:** Ventilated neonates seem to have high oesophageal and LOS pressures that may protect them against reflux. However they exhibit a larger proportion of ineffective oesophageal motor activity. During periods of reflux the oesophagus was cleared efficiently by peristaltic oesophageal contractions.


### 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 affect the occurrence of reflux. The aim of this study was to measure pH at the gastric cardia in ambulant subjects and determine its relations to physiological and pathological reflux.

**Methods:** 17 asymptomatic volunteers (9 males, aged 21–33 years) and 17 patients (11 males, aged 33–53 years) with non-erosive reflux disease were studied. Stationary 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 acid exposure (pH at 2 cm below the LOS) showed marked variability but was again greater in patients than volunteers (table). Transient buffering of cardiac pH was seen in patients during ingestion of meals but rapidly returned to preprandial values. Gastric body acid exposure (pH 10 cm below the LOS) was consistently high and similar in patients and volunteers. Significant buffering was not seen.

<table>
<thead>
<tr>
<th>Abstract 016</th>
<th>% time (pH)</th>
<th>Pre-prandial</th>
<th>Meal</th>
<th>Post-prandial</th>
<th>Supine</th>
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<tr>
<td>Normal</td>
<td>37.0 (5.5)</td>
<td>21.7 (5.5)</td>
<td>35.8 (5.0)</td>
<td>38.3 (5.5)</td>
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<tr>
<td>GORD</td>
<td>80.5 (1.5)</td>
<td>47.2 (3.5)</td>
<td>68.2 (1.5)</td>
<td>57.4 (1.5)</td>
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<tr>
<td>P&lt;0.0018</td>
<td>P&lt;0.005</td>
<td>P=0.0034</td>
<td>P=0.006</td>
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</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 cardiac and distal oesophagus was unclear.

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

**Methods:** Ten healthy subjects were studied using a dual channel pH electrode with 1 cm distance markings. The squamo-columnar junction (Z-line) was marked by attaching metal clips at endoscopy. The pH electrodes were withdrawn by 1 cm increments from the stomach into the oesophagus. The minimum pH at each electrode position, the distance from the nostril to the pH step-up and from the nostril to metal clips (Z-line) shown on X-ray were 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 with the body of the stomach (pH 4.4) (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 squamo-columnar junction.

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

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

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

**Methods:** A prospective randomised cross over trial was undertaken comparing MBDB and RB in patients with <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 quadrants in the case of diffuse and heterogeneous staining Barrett’s segment. RB was done using standard endoscopic biopsy forceps from the four quadrants at 2 cm intervals. Dysplasia was defined as: indeterminate dysplasia (ID), low grade dysplasia (LGD), high grade dysplasia (HGD) and carcinoma (Ca). The histopathologist was blinded (unaware of which samples were methylene blue stained).

**Results:** Fifty-seven patients were recruited, of whom 44 were male. The mean age was 60 years range (31–85). The mean length of Barrett’s was 5.4 cm. Using MBDB 651 biopsies were obtained (mean 11.4, range 3–23). SIM was present in 491 biopsies (75.42%). Dysplasia and carcinoma were diagnosed in 26 patients: ID1, 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 with MBDB. 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 OESOPHAGUS AS IT 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
Cytokines Induce Preferential Squamous Epithelial Cell Repair Following Photodynamic Therapy for Patients with Barrett's Oesophagus: An In Vitro Model

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Background: Photodynamic therapy (PDT) is an emerging endo-scopic treatment for patients with dysplasia in 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/cytokines.

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

Results: In co-culture, squamous cells (OE-21) underwent greater restitution than columnar cells (OE-33). In both mechanical wound and PDT assays of co-cultures, TGF-β1 increased cell repair by restitution compared with controls (p<0.05). This effect was not seen in individually cultured cell lines. KGF and HGF stimulated restitution of squamous and co-culture cells after mechanical injury and also inhibited columnar cells significantly (p<0.05). IL-8 had no effect on cell restitution.

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

Barrett's Surveillance is Worthwhile and Detects Curable Cancers


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

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

Results: Of 23,725 endoscopies, 506 patients were diagnosed as Barrett's oesophagus and 24 (5%) had carcinoma at diagnosis (prevalence cancers). 126 patients had at least one surveillance endoscopy. 248 surveillance endoscopies were performed spanning 338 patient years. 13 surveillance (incidence) cancers were detected. The surveillance cancers were diagnosed within 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 oesophagectomy. All had carcinoma in the resection specimen. Lymph nodes showed evidence of metastases in 1 of the 10 resections. 3 patients in the surveillance cancer group did not have an oesophagectomy. 1 of these patients died. 1 patient in the prevalence cancer group (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 curable cancer was detected per 48 patients of surveillance (338/7).

Conclusion: 5% of Barrett's patients undergoing endoscopy have prevalent cancers. If surveillance is performed, 4% per year (13/338 %) develop cancer and 2 % per year are cured of their cancers. Most surveillance cancers are operable and of those undergoing surgery 70% are cured. Barrett's surveillance is cost-effective compared with other cancer screening or surveillance initiatives.
(ALA) suggest that HGD can be eradicated in 80% of patients. Our aim is to identify parameters associated with successful eradication of disease.

Methods: 15 previously untreated patients (13 M, 2 F) with HGD (11) or T1m AdCa (4) were treated over a 3-year period. Ethical approval was obtained. Patients were photosensitised with ALA 60mg/kg (light activation 635 nm) and received 30 PDT sessions: median of 2 per patient (range 1–3). ALA light doses were 500–1000/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 photosensitizer meso-tetrathydroxyphenylchlorin (mTHPC, 0.15mg/kg).

Results: Disease (HGD 5, AdCa 3) was eradicated in 8 patients (53%): 6 patients (40%) with ALA alone, 2 with additional mTHPC. Median follow-up is 10 months (range 2–29) with no deaths and no oesophageal strictures. One patient developed new HGD 2 years after successful treatment and is being re-treated. Benign glands "burned" under neo-squamous epithelium were seen in 7/15 cases. Failure of treatment was associated with the length of Barrett’s segment (median in responder BARD = 3 cm, non-responders BARD = 8 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 patients. A long Barrett’s segment and multi-focal disease are associated with a poor outcome. Techniques to achieve a deeper effect (such as adding an iron chelator to ALA or using a different photosensitizer) may give better results.

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

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1St James’s Hospital; 2Primary Care Sciences Building University of Birmingham, UK

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, obesity (BMI) > 40, previous upper intestinal surgery and an hiatus hernia > 2 cms. Pre-procedure assessment included symptom scoring, oesophageal endoscopy, manometry and 24 hour oesophageal pH, and completed quality of life (QOL) questionnaire. Post procedure symptomatology, endoscopy, manometry and 24 hour oesophageal pH were measured. Complete follow-up was achieved in all patients.

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

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

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Introduction: Predictive models are increasingly being applied to evaluate surgical performance in upper GI surgery. We describe the use and limitations of hierarchical models in making quantitative comparisons between teaching and non-teaching institutions.

Methods: A longitudinal study of 981 patients undergoing major oesophagogastrectomy from 31 UK hospitals from 1993 to 2000. Primary outcome was inhospital mortality and risk-adjusted mortality. A two-level random effect logistic regression model was developed using age, pre-operative POSSUM and staging as “level 1” (patient) risk factors and teaching unit status as “level 2” risk factors.

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

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

Funding: The Royal College of Surgeons of England.

Gastroduodenal free papers

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

J. Deeks, B. Delaney1, D. Forman1, P. Moayyedi1. ICRF/NHS Centre for Statistics in Medicine, Oxford, UGPD Cochrane Group; 1University of Leeds; 2Primary 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...
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 of 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.

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

H.R. Pearce1, N.J. Brown1, K.D. Bardhan2, J.C. Atherton3, N. Kalia1.

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 observed 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. Cag+ve HVs Cag+ve HVs Cag−ve HVs Cag−ve HVs

**Conclusion:** *H. pylori* extracts inhibit EC proliferation in vitro by a cytostatic 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.

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

D. Gillen, A. Wirz, J.E.S. Ardill, J. Crabtree, K.E.I. McCall. University of Glasgow, Scotland, UK

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

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

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

**029 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 caseloads and revealed an open and close laparotomy rate of 23%. Wider use of laparoscopy was advocated strongly.

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

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

**Results:** See table.

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<td><strong>Stage</strong></td>
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<tr>
<td><strong>Cag+ve HVs</strong></td>
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<td>20pmol/Kg/h</td>
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<td>Sensitivity</td>
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<td>MAO (mmd h−1)</td>
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Values are medians (interquartile range); *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% (Chi2 12.65, P<0.0001) that would have resulted without laparoscopy.
THE EFFECT OF REDUCED QUALITY OF LIFE ON THE SUBSEQUENT DEVELOPMENT OF GASTRICAIDIA AND IRRI table BOWEL SYNDROME: A PROSPECTIVE COHORT STUDY
Gastroenterology Unit, City Hospital, Birmingham; Centre for Digestive Diseases, The General Infirmary at Leeds; Northern and Yorkshire CTRU; Centre for Cancer Research, University of Leeds, UK

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 urea 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), an inventory with items covering 5 domains: energy, positive outlook, relationships, and others. Subjects that had dyspepsia or IBS at baseline were excluded. Reduced QoL was defined as a PGWBI of < 106 (the mean score at baseline). Subjects who 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).

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.

PROTON PUMP INHIBITOR THERAPY REDUCES BIOAVAILABILITY OF DIETARY VITAMIN C
E. Henry, A. Wirz, C. Mowat, V. Fyle, K.E.L. McColl. Dept of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, UK

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 daily. Vitamin C was measured on H pylori +ve and 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 subjects (p<0.001). A mean of 40, 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 (92.5).

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.

WORKLOAD AND TRAINING: AN AUDIT COMPARING THE WORK PATTERNS OF GASTROENTEROLOGY TRAINEES WITH OTHER MEDICAL SPECIALTIES
I.G. Beveridge, I.R. Gooding, M.J. Lockett, J.E.D. Mawdsley. Department of Gastroenterology, St Mary’s Hospital, London W2, UK

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

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

Results: 25 gastroenterology trainees from 14 hospitals (5 teaching, 9 DGH) completed questionnaires. 23 trainees from other medical specialties completed questionnaires.

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specialties in 4 hospitals (1 teaching, 3 DGH) participated. Specialties represented included: cardiology, endocrinology, respiratory medicine, rheumatology and elderly care. Gastroenterology trainees attend a median of 2 clinics (range 2–3) and 3 endoscopy sessions (range 2–5) per week. By contrast other trainees attend a median of 2 clinics (range 1–5) but have only 1 endoscopy session (range 0–2) for other specialty activities (e.g. bronchoscopy, angiography etc.). Gastroenterology trainees had less available time for general ward work and the majority (55%) had no allocated session for administration, teaching or research. 85% of other trainees had at least 1 session allocated for these activities.

Conclusions: Gastroenterology trainees, like their consultant trainees, have work patterns which reflect the increasing pressures on both general medical and gastroenterology services. The “New Deal” and future “working time directives” are likely to affect the provision of services and training in gastroenterology and specialty bodies must consider these pressures in order to continue to provide high quality training in gastroenterology.

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### 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.

**Aims:** (1) To determine whether open access endoscopy identifies significant numbers of patients with malignant upper GI disease. (2) 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 or 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.

<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>
</tr>
</tbody>
</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 is cost effective. Our study suggests that adoption of this policy should reduce the number of endoscopies in young patients.

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### WHY DO PATIENTS FAIL TO ATTEND FOR OPEN ACCESS UPPER GI ENDOSCOPY?

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

**Introduction and aims:** The DNA rate to our GP Open Access Endoscopy Service (OAE) is approximately 15%. We carried out a study to ascertain if those failing to attend had specific characteristics which would allow us to advise GPs which patients might be unsuitable for OAE.

**Methods:** Characteristics of 50 consecutive patients who failed to attend were compared with 50 who attended over the same time period. Both groups completed three questionnaires, namely: (1) Demographic and lifestyle details, including alcohol and cigarette consumption, employment and home circumstances. (2) The modified Glasgow Dyspepsia Scoring Questionnaire, as an index of their dyspepsia. (3) Fear of the endoscopy (where 0 = no fear and 10 = terrified). The DNA group was asked to select an appropriate reason for failure to attend from a list of prepared options.

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

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

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

A. Douglass, P.A. Cann. Endoscopy Centre, James Cook University Hospital, Middlesbrough, UK

**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 attendance rates.

**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 maximisation of hospital appointments demonstrates that allowing patients to choose a convenient date, does result in a significant reduction in DNA and cancella-
tion & rearrangement rates. This not only reduces time wasted in clinics and endoscopy sessions but also by administrative staff, secre-
taries, 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.

A038 AUDIT OF FAST TRACK 2-WEEK GI CANCER WAIT
E. Stoker, A. Elsender, D. Bradford, M. Cullen, V. Chinmoe, N. Thompson. The Newcastle upon Tyne Hospitals NHS Trust, UK

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 take 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 60–79 yrs. Time from referral to initial assessment: upper < 1 week 56 patients (50%), lower < 1 week 54 patients (48.2%), > 1 week 58 (51.8%). In the upper group, 51% were referred by GPs and 39% was 3 years previously. In the lower group, 49.6% were referred by GPs and 40.6% was 3 years previously. The proportion of diagnosed carcinomas is in excess of the expected targets. The 2-week referral system has been successfully implemented despite logistic difficulties, but use of the system by GPs is patchy.

A039 DOES PRECEDEING TREATMENT WITH A PROTON PUMP INHIBITOR (PPI) DELAY OESOPHA-GASTRIC CANCER DIAGNOSIS?
V. Kaushik, J. Limdi1, A. D. Higham. Department of Medicine, Royal Lancaster Infirmary, Ashton Road, Lancaster; 2North Manchester General Hospital, Delaunay’s Road, Crumpsall, Manchester

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

Aim: To determine whether PPI treatment prior to endoscopy results in delay in 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 two 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 hospi-
tal doctor.

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

A040 A 10 YEAR RETROSPECTIVE STUDY OF UPPER GI ADENOCARCINOMA. HOW CAN WE IMPROVE EARLY DIAGNOSIS?
S. J. Panter1,2, H. O'Flanagan3, M. G. Bramble1, A. P. S. Hungin4, 1James Cook University Hospital, Middlesbrough; 2NoReN, Eaglescliffe Health Centre, Stockton; 3CHR, University of Durham

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 because the records did not include information regarding acid-suppressing medication. This left 719 patients. Of these, 357 patients had been prescribed AST prior to diagnosis. A mean of 3.5 years had passed since recording of the most recent prescription was made and 43.7% of these patients had been prescribed AST for >1 year. 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 a previous gastroscopy within 3 years of diagnosis, whereas of the 283 prescribed AST prior to diagnosis this figure was 42.4% (p<0.001). Overall, 39.5% 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 presentation. As 22% had only benign symptoms at diagnosis decisions regarding treatment or investigation should not be based solely upon symptoms but on an overall assessment of risk.

A041 EMPIRICAL ACID-SUPPRESSING DRUG THERAPY (AST) IS ASSOCIATED WITH DELAYED DIAGNOSIS OF OESOPHA-GASTRIC CANCER
S. J. Panter1,2, H. O'Flanagan3, M. G. Bramble1, A. P. S. Hungin4, 1James Cook University Hospital, Middlesbrough; 2NoReN, 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.

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A042 DOES PRECEDEING TREATMENT WITH A PROTON PUMP INHIBITOR (PPI) DELAY OESOPHAGO-GASTRIC CANCER DIAGNOSIS?
V. Kaushik, J. Limdi, A.D. Higham. Departments of Medicine, Royal Lancaster Infirmary, Ashton Road, Lancaster; North Manchester General Hospital, Delaunay's Road, Crumpsall, Manchester

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

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

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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.
PREDICTIVE VALUE OF ALARM SYMPTOMS IN CLO™ TESTING: OPTIMAL NUMBER OF BIOPSIES

Department of Gastroenterology, Stepping Hill Hospital, Stockport, UK

Background and Aim: Alarm symptoms in dyspepsia are thought to predict significant pathology at endoscopy (OGD). However few studies have assessed their predictive value 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), gastric ulcer (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 gastric 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.

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

K.P. Basavaraju, P. Cleary, N.K. Ahluwalia. Department of Gastroenterology, Stepping Hill Hospital, Stockport, UK

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 have recently shown that taking 3 biopsies (2 antral + 1 body=CLO1) is superior to histology (77.5% sensitivity) as well as 2 antral biopsies & all 30 in CLO3.

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

Results: 100 patients underwent CLO testing. 30 patients were CLO positive. Of these 28 were positive in CLO1 & all 30 in CLO3.

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

www.gutjnl.com
Aim: 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 ooze 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 present was clearly seen in 81% of the cases, was highly suspected in 13% and in 6% spurring or ooze bleeding was present. In addition to FG, in 63% and 5% of the cases, adrenaline 1:10,000 and ethanolamine oleate separately 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

M. Inomata, M. Endo, H. Obara, Y. Hashimoto, Y. Miyamoto, S. Oana, T. Terui, T. Chiba, S. Orii, K. Suzuki. First Dept of Internal Medicine, Iwate Medical University School of Medicine, Morioka, Japan

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

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

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

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

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


Background: Acute mediastinitis is a serious complication, occurring after esophageal perforation, thoracic surgery and rarely spontaneously due to infections. Clinical and CT scan signs may be nonspecific, especially in postoperative patients.

Methods: We prospectively evaluated the value of endosonography (EUS) with guided fine-needle aspiration (FNA) in the diagnosis and identification of etiologic agents in critically ill patients with suspected posterior mediastinitis. EUS-FNA was performed at the bedside in the intensive care unit using a Pentax 34UX echoendoscope and a Hitachi console. 18 patients with clinically suspected mediastinitis were examined with intensive care team support. CT was carried out prior to EUS in all 18 patients and was inconclusive in 9.

Results: EUS detected mediastinal lesions in 16 out of 18 patients (89%). Thirteen had recently undergone surgery (10 esophagectomy, 1 other esophageal surgery, 1 head/neck cancer surgery, 1 complication after dilatative tracheotomy, 3 with suspected "spontaneous" mediastinitis). In all 16 patients infectious organisms were detected (bacterial: n=14, fungal: n=1, tuberculosis: n=1). Culture and sensitivity of EUS-FNA specimens lead to appropriate drug-therapy. In two patients MRSA were detected, leading to isolation care. Eleven patients improved, 6 patients died. In two patients, in whom EUS did not detect a mediastinitis, one was a false-negative on autopsy. There were no complications.

Conclusion: Bedside EUS-FNA of posterior mediastinal lesions in critically ill patients was an effective and relatively non-invasive way to detect mediastinitis and provide material to identify the etiologic agent.

ENDOSONOGRAPHY GUIDED FINE-NEEDLE ASPIRATION (EUS-FNA) IN THE DIAGNOSIS OF SMALL SPLENIC LESIONS

A. Fritscher-Ravens, N. Soehendra, P. Swain.

Department of Gastroenterology, Royal London Hospital, London; Dept of Interdisciplinary Endoscopy, University Hospital, Hamburg, Germany

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

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

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

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

Inflammatory bowel disease free papers 049–062

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

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Introduction: Alterations in epithelial glycoprotein expression in inflammatory bowel disease (IBD) include increased expression of the
oncofetal carbohydrate antigens, TF (galactose β1,3N-acetylgalactosamine) and sialyl-Tn (sialyl 2,6N-acetylgalactosamine). Previous chromotographic colonic mucin analysis in monozygotic twins with IBD suggested a possible genetic basis for these changes (Tyrk 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 concordant for UC or CD; 16 healthy twins). Affected twins were in clinical and endoscopic remission. Expression of sTn and TF was assessed by indirect immunohistochemistry using a specific monoclonal antibody and peanut lectin respectively, and compared with expression in rectal biopsies from normal mucosa (irritable bowel syndrome) controls (n=14 sTn; n=17 TF) with investigators blinded for diagnosis. TF positivity was scored from 0 to 3.

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

Conclusions: The positive findings in unaffected twins support previous evidence of a biochemical mucin defect. This could be the result either 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 superior 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 sulfonic 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 1×108 PFU Advmu-10, empty cassette virus (AdvO) or PBS. After 24 hours colitis was induced by two intra-retinal 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 Advmu-10 suffered significantly less weight loss over time than AdvO or PBS controls after TNBS administration (p<0.0001 by 2 way ANOVA). In addition, Advmu-10 therapy led to significant reduction in stool pro-inflammatory cytokine levels and acute phase response. Finally, the histological score of mice with TNBS colitis treated with Advmu-10 was significantly lower than AdvO or PBS treated controls (T1: 1.0±0.9 compared to 10.4±1.0 and 10.8±1.3 respectively; p<0.05). The therapeutic efficacy of Advmu-10 was associated with a decrease in the TNF-α, IL-10 and IL-6 levels detected in colonic homogenates from mice with TNBS colitis. Advmu-10 had no effect on cytokine release from stimulated systemic lymphocytes.

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

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

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

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

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

Results: The NOD2 variants were associated with ileal disease only (P<0.0001; RR=4.1). All 42 patients who possessed Leu1007fsinsC (non-synonymous SNP) had ileal disease (P=0.0001). The risk of ileal disease was greatest in compound heterozygotes and homozygotes (P<0.0001; RR=37.4). Early age of onset was associated with carriage of Leu1007fsinsC (p=0.006) and compound heterozygosity (p=0.03). In contrast alleles on specific extended HLA haplotypes determine overall susceptibility (Cw*0802, P=0.0004, RR=3.05; DRB1*0701, P=0.03, RR=1.61). Association with DRB1*0701 was also observed in familial disease (p=0.03). Genetic comparisons were made between CD patients and healthy controls.

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

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

Aims: To determine whether NOD2 variants are associated with susceptibility to BD and to determine whether HLA-B*51 and NOD2 typing may be used to distinguish BD from CD.

Methods: PCR-SSP was used to determine HLA-B types and NOD2 variants (non-synonymous SNPs - Arg702Trp and Gly908Arg; frameshift mutation - Leu1007fsinsC). 129 Caucasian BD patients, 244 CD patients and 350 healthy Oxfordshire control subjects were studied.

Results: HLA-B*51 was significantly associated with BD only; 32.4% vs. 9.9%; p=2x10^-3. No association was found between NOD2 variants and susceptibility to BD despite stratification by B*51 status. When BD and CD patients were compared possession of a NOD2 variant without HLA-B*51 carried a likelihood ratio (LR) of CD rather than BD of 6.8. Conversely possession of HLA-B*51 without a NOD2 variant carried a LR of 4.7.

Conclusions: (1) Polymorphisms in the LRR of the NOD2 gene, associated with CD, do not confer susceptibility to Caucasian BD. (2) NOD2 and HLA-B*51 typing may be used to molecularly distinguish BD from CD. (3) Polymorphisms in other regions of the NOD2 gene need to be studied in BD before NOD2 can be excluded as a susceptibility gene for BD.
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 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 (Sep-Nov). Seasonal analysis using the von Mises distribution gave a \( \chi^2 = 3.67, p = 0.9 \).

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

BMJ 2001;323:907.

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. 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 (90bmp), temp. (37.0°C) and haemoglobin (12.3g/dl) did not differ significantly among 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 procto-colectomy, 23 had subtotal colectomy. Conclusions: A colectomy rate of 28% for severe colitis across the UK is similar to that reported from single centres. At admission, ESR was more predictive of outcome than CRP. Duration, previous attacks, extent or severity of symptoms on admission did not predict outcome. Recruitment of 116 patients in 3 months makes large trials on severe colitis potentially viable.
NO EVIDENCE OF SEASONALITY IN MONTH OF BIRTH OF BRITISH IBD CASES: A NATIONWIDE PROSPECTIVE POPULATION BASED STUDY OF UNDER 20 YEAR OLDS
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Background: Pre-natal or early neonatal exposures have been postulated to alter the risk of IBD later in life. The risk of Crohn’s disease has been reported to vary with season of birth in cases reported from large UK referral centres. We report birth data from the 1998/9 BPSU-BSGRU UK incidence survey of IBD in those aged less than 20 years (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 a significant better description of the data than a straight line (chi²(6df)=4.11, P=0.6613 for CD, chi²(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.

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 well understood. However, several recent reports have provided strong evidence for a major role by granulocytes and monocytes in the mucosal inflammation and UC relapse. Accordingly, we thought that patients with corticosteroid unresponsive severe UC might respond to granulocyte and monocyte apheresis (GMCAP). For 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 (Adacol-vm). The carriers selectively absorb granulocytes and monocytes. Thirty one patients with prednisolone unresponsive severe UC and 8 corticosteroid naïve 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 Matsu’s 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.

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=20, ages 18 to 72) were identified of whom 17 had Crohn’s disease and 3 ulcerative colitis. All patients had been intolerant of, or had not responded to Azathioprine, and 19 were taking corticosteroids when MMF therapy was instituted. The median dose of MMF was 1.5g/day and mean duration of therapy was 10.7 months. MMF was discontinued in 12 patients 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/COLICLIC/Small bowel free papers 063–076

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 image, colour television transmitter and silver oxide batteries encapsulated in a strong plastic container with a transparent optical dome window. The 50,000 transmitted images are received via an array of 8 aerials and stored on a portable solid-state recorder, which is carried on a belt.

Results: In a subset of 38 patients push-enteroscopy was compared with capsule endoscopy. A bleeding source was discovered in the small intestine in 21 of 38 patients (55%). These included angiodysplasia (11), fresh blood (5), ileal ulcer (1) tumour (2), Meckel’s diverticulum (1) vasculitis (1). Active intestinal bleeding was seen...
THE RELATIONSHIP OF ADULT COELIAC DISEASE SEROPREVALENCE, CORRELATES AND CONSEQUENCES: A COMPARISON OF WHITE CAUCASIAN AND SOUTH ASIAN COELIAC PATIENTS

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

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

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

Results: Eighty seven (66.9%) of the 130 questionnaires were returned -66 from the Caucasians, and 21 from the South Asian patients (p=0.003). Patients own assessment of their strictness to a gluten-free (GF) diet was significantly correlated with both small bowel histological recovery and negative endomysial antibody status among the Caucasian patients (p=0.005 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 of the gluten-free diet (p=0.014). 3.Obtaining GF products on prescription (0.047). 4.Affordability of GF products (p=0.01). 5.Getting sufficient prescription GF products (p=0.017). 6.A detailed explanation of CD by a physician (p=0.006). 7.Having a follow-up small bowel biopsy (p=0.03). 8.Regular dietetic follow up (p=0.01). No factors were identified amongst the South Asians, who were less likely to attend dietetic clinics (p=0.005), or be members of the Coeliac Society (p=0.02) and were more dissatisfied with information provided by doctors (p=0.026) and dieticians (p=0.011) compared with the Caucasian coeliac patients.

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

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

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

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

**Results:**

- **Bass** 0.116 Strong positive
- **Guinness** 0.49 Strong positive
- **Whisky (blend)** 0 Negative
- **Whisky (malt)** 0 Negative
- **Budweiser** 0.029 Positive
- **Newcastle Brown Ale** 0.4715 Strong positive
- **Stella Artois** 0.1578 Positive
- **Coca-Cola** 0 Negative

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

**Aim:** We wished to investigate whether a peptide corresponding to residues 57–75 of A-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 pepticitc tryptic gliadin (PTG) served as a positive control. Twenty to 100mg of the test peptide was studied on a separate occasion, and on the third a negative control peptide from casein, which comprised 20 amino acids incorporating the same residues as the test peptide, but which were in a different order, was assessed. Following sedation, a Quinton hydraulic multipurpose 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. 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 enterocyte surface cell height fell significantly 4 to 6 hours after commencing the infusions with both PTG and the test peptide, compared to the initial biopsy, in all subjects (n=4).

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

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


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

**Conclusion:** 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 DBQ1*02 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.

**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 62–75 of α-gliadin.

**Aim:** We wished to investigate whether a peptide corresponding to residues 57–75 of A-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 pepticitc tryptic gliadin (PTG) served as a positive control. Twenty to 100mg of the test peptide was studied on a separate occasion, and on the third a negative control peptide from casein, which comprised 20 amino acids incorporating the same residues as the test peptide, but which were in a different order, was assessed. Following sedation, a Quinton hydraulic multipurpose 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. 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 enterocyte surface cell height fell significantly 4 to 6 hours after commencing the infusions with both PTG and the test peptide, compared to the initial biopsy, in all subjects (n=4).

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

**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 (15–19.9 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 (16.2vs22.2 kg/m²), BMD (PA Spine T score −1.92 vs 0.2, total WHQ 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 BMI, 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. 8.4yrs p=0.01) and of amenorrhoea (2.6 vs 5.8yrs 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 gastroenterology out patient clinics and the local coeliac society. Median duration on a GF diet was 10 yrs, range 3-33yrs. Dietary calcium and compliance to a GF diet were determined using a 10-day weighed method, Dietetic interview and a diary/record 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 bread/soya products. 42% used the new generation calcium-enriched GF breads. Median contribution of calcium from GF bread was 27% in those using the calcium-enriched GF breads, compared to 8% in those using standard GF breads.

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

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

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

Results: At St Mark’s, 37 patients died on HPN since 1996 and 33 complete sets of notes were traced (89%). These patients had a median age of 58 years (30–77) and a median time on HPN of 543 days (7–677) [20F:13M]. 25 patients (76%) died from their original disease (HPN-disease), 4 (12%) died from complications of HPN (HPN-comp) and 4 (12%) died from other causes (HPN-other). HPN-comp deaths were sepsis (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 [27.5M]. Indications for ITx were recurrent thromboses [4], recurrent central venous catheter (CVC) sep sis [3] and PN related liver disease [2].

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.

OEFS EFTS 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 actions of chow diets and fibre-free semisythetic diet on polyp progression, cell proliferation and crypt fission. The semisythetic diet was then used to investigate the actions of altered vitamin content (lowered to a third of the RDA and a SS diet where the vitamin content was increased fivefold [except for retinol and folate which were doubled]). 60 Min mice and wild type littermates, 4 weeks old, were divided into 4 groups and fed the four diets for 8 weeks. The number and size of polyps in the small and large intestines were scored later (number*volume = burden), as was the number of native mitoses and the percentage of branching crypts.

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

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

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

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We were concerned that gastroenterologists may be putting themselves in a vulnerable position, in terms of clinical risk, by inserting PEGs purely as a service for other clinicians. A questionnaire was therefore sent out to hospitals in the UK to clarify current practice. Responses were received from 196 of 242 units (>80%). The number of PEGs placed ranged from 1 to 100/100,000 population covered/year with a median of 22 with most placed by medical gastro-enterologists. 59% of responding hospitals have a nutrition team but in 22% of these the patients are still assessed for suitability of PEG only by their own team. The endoscopist does not know what team will need to include patients of all ages. Trials of specific treatments should be undertaken and will need to include patients of all ages.
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 may seem to be either appropriate or acceptable. We believe many endoscopists are exposing themselves to potential risk by acting as technicians and feel that national minimum standards should be considered.

**075 COLONIC MUCOSAL INJURY FROM NATURAL AND SYNTHETIC SULPHATED POLYSACCHARIDES**


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Undegraded lambda λ Carrageenan (λCgN) is widely used as a food additive but is chemically related to the pro-inflammatory agent dextran sodium sulphate (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 colon disease activity and mucosal inflammation in 2 species viz mice and rats. λCgN, DSS (1–4%) or drinking water control were administered for 2–72 days to Balb/c mice (n=225) and Sprague-Dawley rats (n=45) which were maintained on AIN76A antioxidant and mutagen-free diet. Disease activity was assessed by stool consistency, blood loss, weight loss and 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 mice function and mucosal injury were dose dependent and increased with duration of exposure. DSS had greater adverse effects on disease activity than CgN in doses of 3–4% in mice and 1–3% in rats.

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

**076 OUTCOMES IN HOME PARENTERAL NUTRITION IN A NATIONAL UNIT**

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Hope Hospital is one of the UK’s two largest units covering patients on Home Parenteral Nutrition (HPN). In 1998 it was decided to review all new patients commencing on HPN, to study morbidity and mortality. A mean of 27 patients started HPN each year and no patients were lost to follow-up.

85 patients commenced HPN between 15th February 1998 and 15th May 2001, aged 19 years 11 months – 76 years 11 months, (mean 50.2 years ± 16.8 months) (50 females). 19 patients were <40 years, 43 were 40–60 years and 23 were >60 years. 76 patients were entirely self-caring for their line and 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, sclerodermat 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. Patients died of malignancy (3 previously recognised and 1 new case), and of unrelated conditions i.e. 3 patients died of their underlying diagnosis and 6 of unrelated causes. No deaths were related to HPN. 19 patients (22.3%) developed a confirmed line complication - 10 (11.8%) with catheter-related 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±1.05months (range 4–21 months). No clear diagnosis was associated with an increased chance of discontinuing HPN, but 10 patients had surgery (9 neoastrastomastis) 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 (50.8 years ± 19.4), but this was not significant.

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

**Colorectal free papers**

**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 to 3x10^-3 M), firstly paired with time controls and then in the presence and absence of N°-nitroarginine methyl ester (LNAME, 100µM), a nitric oxide synthase inhibitor. In a separate series of experiments the effect of sodium nitroprusside, a direct activator of soluble guanylyl cyclase, was examined in the absence and presence of a sub-maximally effective concentration of zaprinast (3x10^-5 M).

**Results:** Zaprinast caused a concentration-related relaxation of the sheep anal sphincter with the highest concentration giving a mean effect of ZAPRINAST 077–090

**NATIONAL UNIT**

F.C. Leslie, M.A. Bradley, J.L. Shaffer. Intestinal Failure Unit, Hope Hospital, Stott Lane, Salford, Manchester M6 8HD, UK

Hope Hospital is one of the UK's two largest units covering patients on Home Parenteral Nutrition (HPN). In 1998 it was decided to review all new patients commencing on HPN, to study morbidity and mortality. A mean of 27 patients started HPN each year and no patients were lost to follow-up. 85 patients commenced HPN between 15th February 1998 and 15th May 2001, aged 19 years 11 months – 76 years 11 months, (mean 50.2 years ± 16.8 months) (50 females). 19 patients were ≤40 years, 43 were 40–60 years and 23 were >60 years. 76 patients were entirely self-caring for their line, 9 requiring input from family or outside care e.g. district nurse. The main diagnoses in these patients were Crohn's (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 of unrelated conditions i.e. 3 patients died of their underlying diagnosis and 6 of unrelated causes. No deaths were related to HPN. 19 patients (22.3%) developed a confirmed line complication - 10 (11.8%) with catheter-related 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 neoastrastomastis) 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 (50.8 years ± 19.4), but this was not significant.

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

**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.

**079** 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, national guidelines will facilitate patient selection for RBCs.

**Methods and Results:** 7597 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). 1.28 (15%) were diagnosed as having colorectal cancer (mean age 70, range 45–90). 390 (15%) patients had polyps (mean age 62, range 19–94) and were referred for formal colonoscopy. A total of 15 symptoms were recorded in these patients and analysed by age and related to age would aid in the diagnosis of malignancy or polyps.

**Discussion and Conclusion:** This study demonstrates and is in agreement with other studies that the symptomatology of colorectal cancers occurs in their early stages 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.

**080** A COMPARATIVE STUDY ON THE QUALITY OF LIFE IN PATIENTS WITH ILEOSTOMY VERSUS COLOSTOMY

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

**Methods:** Life quality of 25 patients with an ileostomy (median age 41 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 (31–70) or poor (0–30). Results: Of the stoma appliance was without much difficulty in 22 (88%) patients with an ileostomy compared with 16 (64%) patients with a colostomy (P=0.09: x²: NS). Effluent was tolerable in 18 (72%) patients with an ileostomy as compared with only 7 (28%) patients with a colostomy (P=0.002: x²). Appetite was not significantly affected in all patients with an ileostomy (100%), compared with 64% of patients with a colostomy (P=0.002: x²), travel by public transport was not affected in 32% of patients with ileostomy of 28% with colostomy (NS), dress in 20% of patients with an ileostomy of 24% with colostomy (NS) and daily activities 28% of patients with an ileostomy of 24% with colostomy (NS). Furthermore, 68% with an ileostomy did not have a problem with personal hygiene, compared with 40% with a colostomy (NS), while 95% with an ileostomy abstained from sexual activity compared with 81% with a colostomy (NS).

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

**081** ADENOMA PREVALENCE AND ILEAL MUCOSA IN POUCH VS NEOTERMINAL ILEUM


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

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

**Results:** Adenomatous polyps were seen and confirmed by biopsy in 17/32 (53%) pouches compared to just 1/32 (3%) adenomatous polyps in the neoterminal ileum of the same patients. The median number of pouch adenomas was 4 (range 1–50) and median size was 3mm (range 1–40mm). 12 patients (76%) had tubular adenomas with mild dysplasia and 5 patients (25%) had adenomas with either...
villous or tubulovillous architecture or moderate dysplasia. There was no severe dysplasia and there were no cancers. Acute pouchitis (median score 1, range 1–5) was found in 5/32 (16%) patients and chronic pouchitis (median score 2, range 1–4) in 18/32 (56%). Chronic pouchitis, score 4, was found in the neo-terminal ileum of 1/32 (3%) patients but in all cases the neo-terminal ileal mucosa was normal. The presence of pouchitis did not predict presence of adenomas which occurred in 9/17 (53%) patients with, compared to 8/15 (53%) without pouchitis.

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

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

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

**Method:** Between November 1997 and May 2000 13 patients (11 males; 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 52 mm Hg – P<0.005 – Wilcoxon Rank Sum test]. Compared with a collected series of stimulated graciloplasty, non-stimulated gracilis transposition showed a comparable improvement in continence scores and anal manometry but revealed a lower overall complication rate. [20% vs 57%; Non-stimulated vs Stimulated].

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

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

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**Introduction:** Obstructive defaecation (OD) is characterised by prolonged straining at stools and a sense of incomplete emptying. This may be secondary to intra-rectal intussusception and rectopexy has been used to correct this abnormality in attempt to improve OD. The accuracy of radiographic and ultrasonographic imaging and CT in were compared with intraoperative findings in 128 patients.

**Aim:** To determine the accuracy of US and contrast radiography in detecting internal fistulae and abscesses complicating CD in patients undergoing surgery.

**Methods:** In this prospective study the results of US, barium radiology and CT in were compared with intraoperative findings in 128 consecutive patients operated upon immediately after complete evaluation of the intestinal tract by colonoscopy and double contrast barium enema, small bowel enteroclysis and abdominal US, as well as CT in patients with clinically suspected septic complications. Results were analysed on a per-patient basis.

**Results:** The accuracy of radiographic and ultrasonographic evaluation of septic complications of CD is still debated.

**Conclusion:** Routine follow-up by MRI can 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.

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

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**Background:** 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-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 were 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 pelvic MRI examination over a median period of 21 months (inter-quartile range 12–27) follow-up. Recurrent pelvic disease was picked up 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 can 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 severe dysplasia. 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 away from higher grade dysplasia.

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

**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 aged 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 IBT 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, 74% had a clearly defined histology. Of the 35 flat & 6 depressed lesions in OCU, 10 (24%) showed severe dysplasia (P) or invasive cancer (I).

**Conclusion:** There was no significant difference in the proportion of flat & depressed neoplasms detected in UK & Japan when the colonoscopy was performed by the same endoscopist using the same definition. 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**

P. Maayadi1, S. Duffett, S. Mason2, J. Brown3, A.T.R. Axon. 1City Hospital, Dudley Road, Birmingham. Centre for Digestive Diseases, Leeds General Infirmary, Great George Street, Leeds, 2NYCTRU, University of Leeds, UK

**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. This randomised controlled trial tests 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 team interviewed subjects with an IBS questionnaire at baseline, 6 months and two years. Participants were defined as having IBS if five or more Manning’s criteria were present.

**Results:** 1,713/2,929 (74%) participants attended at two years with complete questionnaires. 1,439 subjects did not have IBS at baseline and at two years IBS was present in 63/721 (9%) receiving placebo and 41/718 (6%) allocated antibiotics (odds ratio for those taking antibiotics = 0.63; 95% CI = 0.42 to 0.95; p=0.03). Evaluating individual IBS symptoms suggested frequent stool (OR = 0.53; 95% CI = 0.3 to 0.7; p = 0.0) 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).

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

**090 IS THE P53-APOTOTIC PATHWAY SIGNIFICANT IN THE SHORT COURSE RADIOTHERAPY?**

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

**Methods:** 26 patients underwent operation from January 1982 to October 1984 after short course radiotherapy (15 Gy). Patients’ aged between 27 and 77 years (median 57, 1) were male. Tumour stages were (Dukes) A (2), B (11), C (13). Sections of paired biopsies and post-irradiated surgical specimens of each tumour were immunohistochemically stained for p53, Bcl-2, BCL-XI, Bax, Ki67, & P21/WAF1. The proliferative index (PI) was the percentage of cells positive for PI. The TUNEL method was used to identify apoptotic cells, the apoptotic index (AI) being the percentage of positive tumour cells.

**Abstract 088**

<table>
<thead>
<tr>
<th></th>
<th>Polyoid</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

www.gutjnl.com

Gut: first published as 10.1136/gut.50.suppl_2.a1 on 1 April 2002. Downloaded from http://gut.bmj.com/ on September 22, 2023 by guest. Protected by copyright.
Results: After radiotherapy, the average AI increased significantly increased (2.2 v.s 7.5; p<0.01). In contrast, the proliferative activity (PI) decreased slightly (48.3 v.s 42.7; p=0.05). Bax immunostaining was in 3/26(11.5%) of biopsies and in 15/26 (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 (p53L) exhibited a high AI and a low PI, in contrast with those with p53H. Combination of p53 and p21/ WAF1 revealed a subgroup p53(L) / p21/WAF1(+) with the highest AI (10.3) and the lowest PI (30.4) of all subgroups. Considering Bcl2 / Bax balance, tumours with Bcl2 (++) / Bax (+) also showed a high AI (9.7) and the lowest PI (28.5). In contrary, Bcl2(−)/Bax in the p53 (L) 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

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

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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), 156a (cagPAI+, vacA s2/m2) and the VacA and Cag+ 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 Ttest) more than non-pathogenic strain Tx30a. Use of isogenic mutants showed this effect to be CagA-independent but CagA-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 activity of 60190. In the colon, the cytoplasm of pericryptal fibroblasts was prominently stained. In the duodenum, the cytoplasm of Brunners gland cells was stained. The species from IBD and colonic 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 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 colon, ileum, duodenum and stomach. In the colon, the cytoplasm of pericryptal fibroblasts was prominently stained. In the duodenum, the cytoplasm of Brunner's gland cells was stained. The species 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 crohn's disease and ulcerative colitis.

Conclusion: 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.

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

S. Zar, M.J. Benson, D. Kumar. St George’s Hospital Medical School, London, UK

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.

Method: 52 IBS patients [33 diarrhea-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 peanuts (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 of borderline significance (p=0.058). In the C-IBS group, IgG4 titres were significantly higher for pork (p=0.018) and chicken (p=0.038) compared to controls. D-IBS group had significantly greater IgG4 titres to wheat (p=0.023) compared to C-IBS group. The antibody titres to potatoes, rice, and eggs were not significantly different between the three 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 D-IBS group further strengthens this theory.

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

M.A. Taylor1, J.M. Black2, A. Wallace1, M. Harper1, W.D.B. Clements1, N.V. McFerran2, T. Diamond1, M.C. Regan1. Department of Surgery and 2Centre for Peptide and Protein Engineering, The Queen’s University of Bel-

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

**Methods:** Endotoxin specific peptides were generated using biopanning of a pVIII random linear phage library with Lipopolysaccharide from Salmonella minnesota Re995. A test peptide, P6, was developed which was shown to inhibit LPS-induced TNFa secretion by human monocytic cells. Bile duct ligature 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:**

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

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### Abstract O94

<table>
<thead>
<tr>
<th>TNFα</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>T min</td>
<td>LPS alone</td>
</tr>
<tr>
<td>80</td>
<td>4390*</td>
</tr>
<tr>
<td>(4179–4983.8)</td>
<td>(406–3761)</td>
</tr>
<tr>
<td>100</td>
<td>5451*</td>
</tr>
<tr>
<td>(6635–6233.2)</td>
<td>(644.5–4334.5)</td>
</tr>
<tr>
<td>120</td>
<td>4186.5*</td>
</tr>
<tr>
<td>(5406.3–7214.3)</td>
<td>(744.5–5872.5)</td>
</tr>
</tbody>
</table>

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

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### Abstract O96

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


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Evidence exists that CT, LT and Sta mediate intestinal secretion through an enteric neural reflex arc. Enterotoxins may activate a secretory 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 SATO) for 24 h. CT, LT and Sta, (0.01–2.0µg/ml), were added to cultures. Neurite outgrowth in PC12 cells was assessed 48–72 hours, in 10 fields per coverslip and recorded with a Zeiss Axiovert 100 camera. Only cells excluding trypan blue were included in the analysis.

**Results:** NGF induces neurite outgrowth: 60.7% of PC12 cells in the presence of NGF have neurite[s]=1cell 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. 1.0µg/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: 1.0µg/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.

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### Abstract O97

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


1Antigen Presentation Research Group, Imperial College at Northwick Park, St Mark’s Hospital, London, UK

Integrin α4β7 binds to MadCAM-1 and contributes to homing of lymphocytes to mucosal tissues. Monoclonal antibodies to α4β7 ameliorate rat gut inflammation, indicating the functional importance of this homing. Circulating naive T cells express low levels of α4β7 whereas memory T cells comprise α4β7+, primed in mucosal tissues, and α4β7− subsets. Differentiation of α4β7− naive cells into α4β7+ or α4β7 may be influenced by antigen presenting cells, such as the dendritic cell. Induction of α4β7 following activation of mouse cells with the APC-dependent stimulus soluble anti-CD3 was examined. Well, in the analysis.

**Methods:** Flow cytometry using the dye CFSE, which segregates equally between daughter cells at each cell division, was used to distinguish responding cells. Cells expressing α4β7 were identified by double staining with the antibody OX932 and absolute cell numbers determined using flowCount fluorospheres.

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Results: Almost all mouse T cells freshly isolated from mesenteric (MLN) and peripheral (PLN-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<0.001) 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**

S.D. Hearing, C.J. Crowley, T.J. Creed, M.N. Norman, C.M. Dayan. University Division Medicine, Bristol Royal Infirmary, Bristol, UK

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 (IL-2) 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, by 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 (Ics). Ics 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 (Ics <60%) were modulated (in vitro) to steroid-sensitive by the addition of BAS.

**Abstract 098**

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Median Ics (%)</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>78.0</td>
<td>66.1–86.4</td>
</tr>
<tr>
<td>Dexamethasone + Basiliximab</td>
<td>92.3</td>
<td>89.3–95.6</td>
</tr>
</tbody>
</table>

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)**

S.G. Lala, D. Turton, S. Keshav. Department of Medicine, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK

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

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

Methods: We performed in situ hybridisation, using digoxigenin labelled riboprobes, on paraffin embedded intestinal tissue from eight neonates with NEC and four control subjects. Sense and anti-sense probes were used, and macrophages were identified immunohistochemically using an antibody to CD 68.

Results: The intestinal architecture was disrupted in all cases of NEC and necrosis. Lysosomal and Paneth cell markers 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 pneumatisos 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, J.T. McLaughlin, S. Kazmi, A. Varro*, G. Warhurst*, G.J. Dockery*, G. Thompson. GI Science and 1 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 IFNγ, IL-1β and TNFα 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 (Fura2). 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 IFNγ, IL-1β and TNFα for 2 hours produced small increases in basal CCK secretion. IFNγ (6.25U/ml) produced a 38.8±4.6% increase in CCK secretion compared to control (p=0.02), IL-1β (0.125ng/ml) produced a 16.9±1.5% increase (p=0.005) and TNFα (5ng/ml) produced an 13.7±1.83% increase (p=ns). However when a cocktail of IFNγ, IL-1β and TNFα 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 IFNγ, IL-1β and TNFα 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. Pollock, 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-1R1p and A2B5 were examined 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 was determined by expression of the cytokine 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-1R1p, AcPL and MYD88 were detectable in all transformed IEC lines tested. Expression of the receptor subunits 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 was determined by expression of the cytokine exogenous IL-18. Significantly inhibited parasite development (p<0.0001)

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

RCGP funded by a Wellcome Trust Research Training Fellowship.

MORBIDITY AND MORTALITY REDUCTION USING NITAZOXANIDE IN ZAMBIAN CHILDREN WITH CRYPTOSPORIDIOSIS: A RANDOMISED CONTROLLED TRIAL

B. Amadi1, M. Miwiyia1, J. Musuku1, A. Watuka1, S. Sianongo2, A. Ayoub4, St Bartholomew’s & The Royal London School of Medicine and Dentistry; University of Liverpool, Liverpool L69 3BX, UK

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-1R1p and A2B5 were measured by semi-quantitative PCR in the transformed IEC lines Caco-2, HCT-8, and HT-29, and HT-29 and freshly isolated human IECs. The specificity of the PCR reaction was confirmed by restriction digest or sequence analysis. The action of a panel of proinflammatory cytokines on receptor sub-unit expression by IECs was similarly determined. Finally, the action of exogenous IL-18 (2-200 ng/ml) on C. parvum development in IECs was studied using a previously described in vitro model of infection (Gastro 119: 1234).

Results: Transcripts of IL-1R1p, 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 was determined by expression of the cytokine exogenous IL-18. Significantly inhibited parasite development (p<0.0001)

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

RCGP funded by a Wellcome Trust Research Training Fellowship.

SPECIFIC CYTOTOXIC T LYMPHOCYTE IMMUNITY AGAINST TELOMERASE IN COLORECTAL CANCER

L. Titu, R.L. Loveday, R.P. Baker, J. Greenman, J.T.T. Monson. Academic Surgical Unit, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire HU16 5SQ, UK

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.

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 3 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 (Swidsinski et al. Gastroenterol. 1999;115,281). Such bacteria have been identified 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 biopsy tissue 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, Gaal1-3GalNAcα.

Abstract 104

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Cancer (tumour) n=19</th>
<th>Cancer (distant mucosa) n=19</th>
<th>Normal n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa-associated</td>
<td>14 (74%)*</td>
<td>10 (53%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Intra-epithelial</td>
<td>11 (58%)†</td>
<td>6 (32%)</td>
<td>7 (29%)</td>
</tr>
</tbody>
</table>

Data expressed as number of cases from each group positive for any bacterial growth. Significant difference from normal, p<0.004, †p<0.04.

Results: A significant increase of mucosa-associated and intra-epithelial bacteria was found in colon cancer [see table]. 73% of intra-epithelial bacteria were identified as being Gram-negative (mostly E. coli), bacteria found in 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.

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

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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 contraceptives use (OC), 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 1.2, 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 greater 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 (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%).

Conclusion: 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 intramucosal bacteria, may inhibit neutrophil and macrophage function within the mucosa, leading to the granulomatous lesions seen in CD.

Methods: The effect of S. cereviseiae 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.

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

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

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

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

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

Conclusion: 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 caustion of IBD.
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**107A** 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 splenocytes secreting 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 immunoregulatory changes and to assess its therapeutic efficacy in IL-10-/- mice with established colitis.

**Results:** A single rectal infusion of 5x10⁶ PFU AdvmuIL-10 to 10 week IL-10-/- mice induced a median of 27.3 pg/mg IL-10 in colonic homogenates harvested after one week. In contrast, the IL-10 concentration of liver and spleen homogenates did not differ significantly from the background seen in PBS treated controls. IL-10-/- mice with established colitis were treated with 5x10⁶ 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 1.8 ± 0.27 to 2.5 ± 0.27 and from 1.8 ± 0.22 to 2.6 ± 0.13 in the PBS and Adv0 treated groups respectively (p<0.001, 2-way ANOVA). In addition, the stool concentration of IL-10 over the four-week treatment period 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 with intravenous administration. Gene therapy strategies using adenoviral vectors encoding immuno-regulatory cytokines may prove to be a potent approach to the treatment of chronic inflammatory diseases such as Crohn’s disease.

**107B** 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 (-1031, -863, -857, -308). Two independent cohorts were used (set A, 457 IBD families: 294 Crohn’s disease (CD) trios, 252 ulcerative colitis (UC) trios; set B 130 IBD families and 278 healthy controls (HC)). Functional studies of -857C/T used: LPS stimulated whole blood TNF ELISA in 46 healthy controls; monocyte nuclear extract/promoter construct electro-mobility shift assays; in vitro GST pull-down assays of transcription factors OCT1, NF-KB, and deletion mutants; in vivo COS transfection electro-mobility shift assays; in vitro GST pull-down assays of transcription factors OCT1, NF-KB, and deletion mutants; in vivo COS cell immuno-precipitation and COS cell luciferase reporter gene analysis.

**Results:** TNF -857C was associated with IBD in both set A and replication set B, using case control and family based (TDT) association analyses. Numbers homozygous for TNF-857C were IBD=90.9% (n=567 unrelated cases, P=0.001 vs HC 83.1%), NOD2 negative CD=92.1% (n=241 vs HC=92.1% P<0.001). 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.

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**108** 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, they are more efficient at draining localized lymph nodes and are less susceptible to rejection. 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 receptor 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 the 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-derived DCs secreted IL-2.

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-10.

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.

**109** 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 MPM-9 gene using a SSCP/PCR method. PCR products were run on 1% agarose gels and read under UV light. PSC and UC patients were compared with controls using 2Χ2 contingency tables and a χ² test (with Yates correction). A Bonferroni correction for multiple comparisons was made using a factor of 8 (the number of polymorphisms tested).

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

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

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

R. Buckland, K.L.E. Dear1, A.C. Goodeve, J.C.E. Underwood2, D. Gleeson3. Division of Genomic Medicine and 2Dept of Pathology, University of Sheffield; ‘Liver Unit, Sheffield Teaching Hospitals, Sheffield, UK

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

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

**Methods:** We studied (a): blood (2 extractions x 2 PCR= 4 PCR) from 55 women with PBC and 49 normal control women (irritable bowel or G-O reflux; normal liver enzymes) and (b): archived needle biopsy (1 extraction x 2 PCR = 2 PCR) from 42 women with PBC, 21 women with normal liver histology or mild steatosis (normal controls), and 32 women with autoimmune hepatitis (AIH) (disease controls). All had had >1 male child and none met ARA criteria for scleroderma or had had a blood transfusion or a liver transplant when they were studied.

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

<table>
<thead>
<tr>
<th>Blood</th>
<th>PBC</th>
<th>Normal</th>
<th>Liver</th>
<th>AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>27 (49)</td>
<td>19 (35)</td>
<td>13 (27)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Normal</td>
<td>13 (27)</td>
<td>15 (31)</td>
<td>10 (24)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Liver</td>
<td>1 (2)</td>
<td>10 (24)</td>
<td>31 (74)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>AIH</td>
<td>3 (14)</td>
<td>7 (33)</td>
<td>31 (74)</td>
<td>0 (0)</td>
</tr>
</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:** Non-alcoholic 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 (FAA) to the liver, which in turn may increase hepatic glucose output. Insulin processing involves enzymatic conversion of proinsulin to insulin through a series of site-specific cleavages. Recent development of specific assays allows different molecules of the proinsulin processing pathway to be measured separately. 31,33 split proinsulin is the predominant form of proinsulin, known to be elevated in T2DM and impaired glucose tolerance. Fasting levels have also been shown to predict development of T2DM.

**Methods:** We measured fasting insulin, intact proinsulin and 31,32 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 +/- 2.68 mU/L vs 9.07 +/- 1.18 mU/L, p<0.0014 and higher 32,33 split proinsulin levels: 18.50 mU/L +/- 1.85 mU/L vs 8.55 +/- 0.73 mU/L, p<0.0003. The NAFL group were also significantly insulin resistant using HOMA, p<0.0015. These results were independent of BMI and body fat assessed by BIA.

**Conclusions:** NAFL is associated with hyperinsulinaemia, elevated 31,33 split proinsulin levels and insulin resistance. Patients with NAFL are at increased risk of developing T2DM. Measurement of 31,33 split proinsulin may help to select individuals with the highest risk of 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 FIBROSIS**

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

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

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

**Results:** TIMP-1 and 2 demonstrated a consistent, significant and dose dependent anti apoptotic effect on HSC activated in tissue culture. A non-functional mutated TIMP-1 (T2G mutant) did not inhibit apoptosis indicating that inhibition of apoptosis was mediated through MMP inhibition. Studies of experimental liver fibrosis in the rat demonstrated that loss of activated HSC correlated with a reduction in TIMP-1 mRNA expression by PCR. Persistence of high TIMP-1 mRNA expression in more advanced fibrosis correlated with persistent TIMP-1 mRNA expression. After induction of fibrosis in vivo, TIMP-1 knockout mice demonstrated significantly more HSC apoptosis relative to wild types 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) cycloxygenase was investigated using immunocytochemistry.
We have shown that COX-2 was completely absent from the control group but was highly expressed in the cirrhotic livers. COX-2 was seen mainly in the inflammatory cells infiltrating the liver, sinusoidal cells, vascular endothelial cells and epithelial lining of bile ducts. On 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.

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


Several mediators of systemic vasodilatation in liver cirrhosis have been reported. Among these is nitric oxide (NO), which has been proposed as one of the 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) were measured using Griess reaction and the protein expression of the inducible nitric oxide synthase (iNOS) and constitutive nitric oxide synthase (eNOS) was investigated using immunocytochemistry. We have shown that the serum nitrite levels (94 ± 11.03 µmol/L) in cirrhotic patients were significantly (P < 0.05) increased by comparison to the control (36.6 ± 1.13 µmol/L). iNOS was completely absent from the control group but was highly expressed in the liver of the cirrhotic group. iNOS was seen mainly in the inflammatory cells infiltrating the portal tracts, blood monocytes, hepatocytes, sinusoidal cells and vascular endothelial lining. However, expression 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. eNOS 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 rate of cirrhosis.

**115** SPLENOIC VASCULAR HYPOREACTIVITY IN HUMAN CIRRHOSIS IS RELATED TO DISEASE SEVERITY AND MEDITATED 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 hyperdynamic vasodilatation. The effect of disease severity on in vitro 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=8) and from organ donors and patients undergoing hepatic resection (controls: n=6). Decompensated cirrhosis was defined as Child Pugh score > 8 (n=5) and compensated cirrhosis ≤ 8 (n=4). The response to 80 mmol/L potassium chloride was recorded. Rings were then incubated with either 0.1 mM L-NMMA (a non-selective nitric oxide synthase inhibitor), 0.1 mM ZnPP (a non-selective haem oxygenase inhibitor) or vehicle control for 30 min. Cumulative dose response curves to phenylephrine (PHE) were constructed.

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

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


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

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

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

**Methods and Results:** HepG2 cells were cultured in media supplemented with 10/20% ALF or Normal human (NS) serum. Culture with 20% ALF serum led to significant increases in apoptotic cell death (Feulgen staining/TEM) after 24 (4%) and 48 (7.5%) hrs compared with negligible levels of apoptosis seen in culture with NS. Cellular adhesion (attachment to collagen coated plates after culture in either ALF or NS) was significantly decreased in cells grown in ALF serum. Of note this effect became pronounced after just 4 hours culture, well before apoptosis was observed (see table). Using Scanning Electron Microscopy cells cultured in ALF serum were strikingly more rounded in appearance and appeared far less adherent. Flow cytometric expression of the common integrins (β1, α5, αv, α6) on HepG2 cells was carried out, and after 24 hours culture levels were seen to be higher on cells cultured in ALF serum (β1 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).

**Abstract 116**

<table>
<thead>
<tr>
<th>Culture duration</th>
<th>20% Normal serum (NS)</th>
<th>20% ALF serum (ALF)</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>48 hours</td>
<td>80.3 +/- 11.3</td>
<td>30.3 +/- 7.6</td>
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www.gutjnl.com
Conclusion: Down-regulation of β1-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.

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 Transplant Unit (SLTU).

Methods and Results: We prospectively studied 96 samples from 42 patients, 32 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 prothrombin criteria. 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 higher PT values than the Manchester measured PT, and thus usage of the Innovin PT could potentially lead to patients not being considered for liver transplantation as they would not meet KCPP criteria. Indeed in our cohort no patients had an Innovin PT of greater than 1.141 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.

PENTOXIFYLLINE IMPROVES SHORT TERM SURVIVAL IN SEVERE ACUTE ALCOHOLIC HEPATITIS

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

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

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

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

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 Coroner’s death register were reviewed.

Results: There were no significant differences between the two groups as regards the demographic and clinical criteria or laboratory values, with the exception of an elevated serum creatinine on admission, development of hepato-renal syndrome and the treatment group compared with 80% of the control group. Serum creatinine on admission, development of hepato-renal syndrome and the treatment group compared with 80% of the control group. Serum creatinine on admission, development of hepato-renal syndrome and the treatment group compared with 80% of the control group. Serum creatinine on admission, development of hepato-renal syndrome and the treatment group compared with 80% of the control group.

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.

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 GOV 2 in the glue group (p=NS). In the TIPS group, 15/20 patients had the procedure within 24 hours of haemorrhage and 90% of stent insertions were successful. Complications consisted of three cases of pulmonary oedema, two cases of severe encephalopathy and a 15% stenosis rate at 6 months. In the glue group, there were 3±1.5 endoscopies and 2±1 injections per patient with a 96% haemostasis. There was one case of fatal (glue)
Genetic Haemochromatosis (GH): Where are all the patients?

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

Aims: To (1) estimate the gene frequency of the C282Y mutation in healthy control populations in Glasgow; (2) establish the prevalence of 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 1st 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.

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 were recognised. This represents 4.9% (240 / 4942) of the estimated number of C282Y homozygotes in the area.

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

Hepatitis C: Why have so few patients been treated?

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

A retrospective review of all HCV positive patients attending an outpatient liver clinic was conducted to determine the number who commenced anti-viral therapy and the reasons why patients did not. From Oct 1994-Dec 2000 all those attending clinics were documented. Those seen from Oct 1994 - Oct 1997 were reviewed in detail to determine the reasons why patients did not receive treatment (see table).

Of 490 HCV patients (298M/192F) seen from Oct 1994-Dec 1997, 174 received anti-viral therapy (interferon alone or with ribavirin) and 316 did not. 27% of females were treated compared to 41% males. Predominant risk factors for HCV in either group were IVDU (63%) and 85 blood products (17%). Primary reasons for not receiving therapy: 105 (35%) did not meet Government criteria, 67 (21%) last to follow up after visit 1 or 2, 34 (11%) health, 45 (14%) herbal, 22 (7%) social and 23 (7%) chose no treatment. Of the 1104 patients seen over the 7 years, only 405 (37%) received anti-viral therapy.

Conclusions: 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.

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 (P<0.001). Hypercholesterolaemia was present in 16 % before and 60 % after transplant (P<0.001). 29 % were overweight at the time of transplant compared with 55 % after transplant (P<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 categorise 10-year coronary risk (on the basis of total cholesterol:high density lipoprotein cholesterol ratio, systolic blood pressure, smoking, diabetes mellitus, age and gender) as <15 %, 15–30 % and >30 %. Using these charts we categorised coronary heart disease risk before and after transplant (see table). If we assume patients require therapeutic intervention aimed at 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 (ISEMF) are found in the lamina propria of the intestine under the epithelial cells, and are of critical importance in epithelial-mesenchymal interactions. It has been suggested that the origin of ISEMFin the small intestine and colon could be seen surrounding crypts in both the small intestine and colon. These columns appeared to extend into the villi in the small intestine. In the human intestine we confirmed that the bone marrow-derived cells within the intestine exhibited a myofibroblast phenotype. 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 pericyelial myofibroblasts could be seen surrounding crypts in both the small intestine and colon. These columns appeared to extend into the villi in the small intestine. In the human intestine we confirmed that the bone marrow-derived cells within the intestine exhibited a myofibroblast phenotype.

**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**

J.T. McLoughlin,7 N.F. Sinclair,8 R. Callucci,8 R. Raychowdhury, T.C. Wang,8 T.J. Koh [introduced by Q Aziz1], 1GI Sciences, Hope Hospital, Salford; 2Division of Digestive Diseases and Nutrition, University of Massachusetts Medical School, Worcester MA, USA

**Background:** The gastrin 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 effects of PACAP on this regulatory sequence and the signalling pathways responsible.

**Methods:** 1.88B of the histidine decarboxylase promoter was located into a luciferase reporter-constructor construct and transiently transfected into PC12 cells, either wild type or stable transfectants expressing the gastrin-CK receptor. The effects of PACAP and gastrin on promoter activity were assessed via a series of 5' deletions and other appropriately derived constructs. Classical signalling pathway inhibitors were also used (H7 to block PKC, 698 to block PKA).

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

**Conclusion:** The data show that discrete neural and endocrine pathways impinging on histaminergic cells can exhibit different patterns of post-receptor signalling and promoter element activation. As previously described, the PACAP receptor is able to activate both PKA- and PKC-dependent pathways. A newly characterised PRE in the promoter is pivotal in PACAP’s effect on the HDC promoter, and quite distinct from the gastrin response-elements which have been localised to the +1 to +88 region of the first untranslated exon.

JMc supported by MRC Travelling Fellowship and DDF Senior Fellowship.

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


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

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

**Results:** The gene array revealed PAI-2 as a major, previously uncharacterised, gastrin-regulated gene in AGS cells. The relevance was confirmed by showing significantly (<p<0.05, t test) elevated PAI-2 in plasma of hypergastrinaemic patients (pernicious anaemia (PA)): plasma gastrin, 1.2±0.16 nM, plasma PAI-2, 1.4±0.3 ng/ml, n = 9; multiple endocrine neoplasia type 1 (MEN-1): gastrin, 0.5±0.09 nM, PAI-2, 2.0±0.2 ng/ml, n = 5; MEN-1 patients, but was at or below the limit of detection in 9 of 11 controls. To examine cellular control mechanisms we transiently 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 minichromosome (which is mutated in MEN-1) significantly inhibited gastrin-stimulated PAI-2 expression (p<0.05).

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

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

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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 paracline 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 rinterferon 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-activated 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 cytokeratin 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 agar, 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-induced IEC-6 cell changes.

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

**128 AN N-TERMINALLY TRUNCATED CYTOPLASMIC FORM OF OXYGEN-REGULATED PROTEIN 150 (ORP150), THE MAJOR INTRACELLULAR LIGAND FOR THE ANGII 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 (ABU) (Cancer Res 1993;53:4627) is linked to its internalisation and selective blockade of NSL-dependent nuclear protein import (J Biol Chem 1999;274:4890). One of the major intracellular AB-binding ligands is a N-terminally truncated cytoplasmic form of Orp150 [Gastroenterology 2001;120(suppl1):3579]. Orp150 is a stress-related protein and is up-regulated in tumours and highly expressed in cancer cell lines. In this study we investigated the role of Orp150 in nuclear protein import.

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

**129 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 (MSH4).

Aims: To investigate the heterogeneity of MSI and K-ras and p53 mutations in contiguous SA/CRC and contiguous HP/SA to help understand the timings and genetic mechanisms driving the serrated pathway.

Methods: Paraflag-included 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 SAs had the same K-ras mutation (1/4 PCR failure). The remaining 7 SA/CRCs were wild type. P53 results were available in 10. All 10 CRCs and 5/10 contiguous SAs showed accumulation of mutant p53. Neither of the two HP/SAs showed MSI or K-ras mutations.

Conclusions: All contiguous SA/CRC or HP/SA were concordant in MSI 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.

**130 TELOMERASE EXPRESSION IN BARRETT’S, OESEPHAGEAL AND GASTRIC ADENOCARCINOMA**

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Ribonuclease protein 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 cancers.

Methods: hTERT mRNA was quantitated using real-time RTPCR 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, 5.2 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.

**131 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 oesophagus and examine if TNF-α can promote β-catenin-mediated transcription of oncoproteins 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-kB activation.

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

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

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

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

**Aims:** To investigate the expression of erbB2, src and met along the metaplasia – dysplasia – carcinoma sequence.

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

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

**Conclusions:** The increased expression of met is an early step in the metaplasia – dysplasia – carcinoma sequence. The increased expression of src and erbB2 appears to be later steps in the sequence akin to EGFR. The altered expression of met, erbB2 and src suggests that whilst there may be some redundancy in tyrosine kinase signalling, one of these could provide a mechanism that promotes the progression from metaplasia to carcinoma, and may be a potential therapeutic target.

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

P. Sirieux1, T.K.L. Wong1, L.B. Lovat1, R.C. Fitzgerald1. 1National Medical Laser Centre, Department of Surgery, Royal Free and University College School of Medicine, London; 2Cancer Cell Unit, Hutchison/MRC Research Laboratory, University of Birmingham, Edgbaston, UK

**Background:** Oesophagitis has a Th1 cytokine profile in contrast to Adenocarcinoma arising from Barrett’s oesophagus is characterised by progression along the Barretts metaplasia – dysplasia – carcinoma sequence. The increased expression of met is an early step in the sequence. The altered expression of met, erbB2 and src suggest 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.

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

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**Background:** Acidification of nitrate in the presence of nitratable 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 nitrate (NO3−), derived from dietary nitrate (NO3−), and swallowed saliva is the main source of NO in the stomach. 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.

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

**Results:** The NO3− ingestion increased median saliva 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).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Normal</th>
<th>Cardia</th>
<th>Distal stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>16 fold increase</td>
<td>16 fold increase</td>
<td>16 fold increase</td>
</tr>
<tr>
<td>TGFβ</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>IL-8</td>
<td>1.3 fold increase</td>
<td>1.3 fold increase</td>
<td>1.3 fold increase</td>
</tr>
<tr>
<td>IL-6</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>AA</td>
<td>3 fold increase</td>
<td>3 fold increase</td>
<td>3 fold increase</td>
</tr>
<tr>
<td>NO3−/AA ratio</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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</table>

**Conclusions:** 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.

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

E. Cheong1, 2, K. Ivory1, M. Parker1, M. Rhodes1, T.J. Johnson1. 1Institute of Cancer Research, Park Royal, London NW10 7JU, UK; 2Norfolk and Norwich University Hospital, Colney, Norwich NR4 7UA, UK

**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>
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<th>Cytokine</th>
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<tr>
<td>NO3−/AA ratio</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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

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

Results: Western blot analysis confirmed COX-2 expression in the OE-33 cell line. The selective COX-2 inhibitors and quercetin suppressed OE-33 cells proliferation in a dose- and time-dependent manner, and increased the fraction of floating cells in the population. The majority of the floating cells were identified as apoptotic. The anti-proliferative effects induced by quercetin were significantly greater, and the number of floating cells was significantly higher after quercetin treatment compared with the selective COX-2 inhibitors (p<0.05). Cell cycle analyses revealed that quercetin blocked the cell in S phase while the selective COX-2 inhibitors (NS-398 and Niflumic acid) blocked the cell in G2/M and 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.

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

P.A. Clarke, S. Evans, D. McWilliams, S.A. Watson. Cancer Studies Unit, University of Nottingham, Nottingham, UK

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 modulates endothelial vessel formation of human umbilical vein endothelial (HUVEC) cells in in vitro culture.

Methods: HUVEC cells were grown in a mixed culture system with irradiated feeder cells in 24-well plates. Amidated human gastrin-17 (G17) and glycine extended G17 were added to the cultures at concentrations of 10^{-6}M. Vascular endothelial growth factor (VEGF, 2ng/ml) and suramin (20μM) were used as positive and negative controls, 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 (1.2)</td>
<td>20.5 (1.3)</td>
</tr>
<tr>
<td>Suramin</td>
<td>5.9 (0.5)</td>
<td>6.2 (0.4)</td>
</tr>
<tr>
<td>VEGF</td>
<td>29.5 (1.8)</td>
<td>33.5 (1.7)</td>
</tr>
<tr>
<td>G17</td>
<td>30.0 (2.1)</td>
<td>27.0 (1.6)</td>
</tr>
<tr>
<td>GlyG17</td>
<td>31.0 (1.7)</td>
<td>35.0 (1.7)</td>
</tr>
</tbody>
</table>

Discussion: Mutated p53 accumulation is strongly associated with gastric adenomatosis, its presence being detectable in a far greater proportion than in gastric carcinomas and normal gastric tissue. This pattern of p53 expression matches gastric lesions that seen in the adenoma-carcinoma pathway in the colon than the more common metaplasia-dysplasia-carcinoma pathway that occurs in the stomach.

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

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

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

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

Method: 15 Sequential archived paraffin blocks taken from gastric resections and endoscopic biopsies of gastric adenomas were analysed by immunohistochemistry using a monoclonal antibody raised against p53 clone DO-7 protein (Dako). An avidin-biotin bridge and DAB detection system were employed (Vector). Positive controls from an oesophageal carcinoma (Dako) and negative controls of 15 normal aged matched gastric sections and replacement of the primary antibody with serum from the host animal were employed. 15 sections from unselected gastric adenocarcinomas were also analysed. 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>
</tbody>
</table>

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

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

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

Methods: Thirty-six sequentially presenting patients undergoing surgery for colorectal cancer and ten healthy controls were included in the study. Patient blood samples were taken pre-operatively, and 1 and 7 days post-operatively. Peripheral blood mononuclear cells (PBMC) were obtained from whole blood by Ficoll-Hypaque density gradient centrifugation. Circulating epithelial cells were then isolated from PBMC by incubating with the epithelial specific antibody BerEP4 conjugated to magnetic beads. Cells were harvested using a magnetic field, lysed and protein content determined and standardised. Telomerase activity was detected in lysates using TelTagg Telomerase PCR EUSA (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
introduction of tumour cells into the circulation. For 11 (67%) of these patients the CTC were still detectable at 7 days after surgery. The presence of telomerase positive CTC did not correlate with the cancer’s stage. None of the healthy controls exhibited telomerase activity in epithelial cells.

Conclusions: The method described represents a simple and specific method for the detection of CTC in colorectal cancer patients. The detection of telomerase activity in CTC may have important implications in the treatment of CCK-BR positive tumours (Watson et al., 2000). We have previously found that cell lines exposed to an antibody raised against a peptide corresponding to residues 5–21 of the amino terminus of the CCK-BR display endocytosis of the antibody into the cytoplasm and nucleus.

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

Methods: The anti-CCK-BR antibody was labelled with Alexa Fluor 488 dye (Molecular Probes, USA). HepG2 (human hepatocyte carcinoma), PLC/PRF/5 (human liver hepatoma), MCA RH 7777 (rat hepatoma), PLC/PRF/5 (human liver hepatoma), MCA RH 7777 (rat hepatoma), HTC (rat hepatoma) and WRL 68 (human liver embryonic) cells were exposed to the labelled antibody at 20 µg/ml for 1 hour at 37°C. The cells were fixed and subsequently 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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INTERCOLLEGIATE-BSG NATIONAL COLONOSCOPY (IBNC) AUDIT: THE CONSENT PROCESS PRIOR TO COLONOSCOPY AS REPORTED BY A PATIENT QUESTIONNAIRE

C. J. A. Bowles 1, R. Leicester 2, E. Swarbrick 3, C. B. Williams 4, C. Ro maya 5, M. Stubbs, K. Khan, K. Savage, S. Grimes, D. Michaeli, A. P. Dhillon, S. A. Watson, M. E. Caplin. Royal Free and University College Medical School, Pond Street, London NW3 2PF, UK

Background: It has been reported that administration of an anti-CCKB/gastrin receptor (CCK-BR) antibody to mice bearing human xenograft tumours results in increased apoptosis and necrosis (Watson et al., 2000). 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 the endocytosis of this anti-CCK-BR antibody correlates with the occurrence of apoptosis in these same cell lines.

Methods: The anti-CCK-BR antibody was labelled with Alexa Fluor 488 dye (Molecular Probes, USA). HepG2 (human hepatocyte carcinoma), PLC/PRF/5 (human liver hepatoma), MCA RH 7777 (rat hepatoma), PLC/PRF/5 (human liver hepatoma), MCA RH 7777 (rat hepatoma), HTC (rat hepatoma) and WRL 68 (human liver embryonic) cells were exposed to the labelled antibody at 20 µg/ml for 1 hour at 37°C. The cells were fixed and subsequently 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.

DO ALARM SYMPTOMS IN DYSPHAGIC PATIENTS WARRANT URGENT UPPER GI ENDOSCOPY?

C. Mowat, M. McKernan 1, J. Morris. Dept of Gastroenterology and Surgery, Glasgow Royal Infirmary

Introduction: Direct access endoscopy referral forms have been used by local GP’s for 2 years. The local Dysphagia Management Guideline recommends urgent referral for dysphagic patients with dysphagia, weight loss, anaemia, recurrent vomiting. There is little guidance 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/duodenitis, 39 had oesophagitis alone, 20 had peptic ulcer, 5 (1.8%) gastric cancer, 7 (2.5%) oesophageal cancer, 9 (3%) had Barrett’s. None of the alarm symptoms were predictive of a particular diagnostic finding. Over the study period, a total of 67 upper GI cancers presented to the hospital (28 oesophageal, 32 gastric, 2 duodenal, 3

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pancreatic, 2 incomplete data); mean age 73 (46–90). Only one patient was aged less than 55, 26 of these were presented via other direct access routes. The remaining presented via A&E or clinic. 12 of 38 patients referred urgently versus 2 of 22 in-hospital referrals were suitable for attempted curative surgery. Of the 14 suitable for surgery, mean age was 68 (58–75).

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 dyspeptic 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.

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

C. Roseveare1, 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 set-up and supervised by an endoscopy nurse and endoscopist.

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

Results: Sedation method had no impact on the success, difficulty or duration of the colonoscopy procedure. PCS infusions could be set up by the endoscopy nurse without causing significant delay. Patients in the PCS group recovered significantly faster (mean 5mins vs 35mins, p<0.0001) and left the endoscopy department much sooner (40mins vs 75mins, p<0.0001). No differences in respiratory or haemodynamic observations were recorded between the two groups. Anaesthetist intervention was required for one patient sedated with M&P, but was not required for any patients sedated with PCS. Overall sedation level was lighter in the PCS group (score 3 vs 4, p<0.05) and verbal contact was lost with only 2 patients using PCS, compared to 9 using M&P. Patients in the PCS group reported significantly more pain (median pain score 1 vs 0, p=0.0005), which may have reflected the greater chance of attempted curative surgery. Rapid assessment of the sigmoid colon was determined in 82 patients. Two insertions were performed in each patient, from the mid-descending 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.

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

145 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 the shaft to prevent looping after 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 CF-Q240AL) in the mid-descending colon was determined in 82 patients. Two insertions were performed in each patient, from the mid-descending 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 manoeuvers 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 manoeuvers performed were fewer (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 and its 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.
146 THE EFFECT OF TEMPERATURE ON THE FLEXURAL RIGIDITY OF VARIOUS COMMERCIALY AVAILABLE COLONOSCOPIES AND GASTROSCOPES

S. Dogramadzi, R. Burn, R. Bicker, G.D. Bell. Department of Electrical and Electronic Engineering, Newcastle University; School of Computing, Engineering and Technology, University of Sunderland; Department of Mechanical Materials and Manufacturing Engineering, Newcastle University; Medical Sciences Faculty, Sunderland University

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

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

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

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

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

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

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

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

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

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

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

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

Methods: Consecutive 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 for “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 technique involved applying 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 technique involved applying 2L/min gas flow; 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).

Results: From 505 examinations [237 male, median age 55[19–93]], 40 suitable adenomas (median size 7mm[4–5mm]; histology: 33 tubular, 7 tubulo-villous) were identified in 23 patients [19 males; median age 55(19–93)]. 20 were treated with APC and 20 with “hot-biopsy”. There were no complications. At follow up colonoscopy, a median of 6.4 weeks later (range 3–11 weeks) there were two recurrent adenomas following “hot-biopsy”, but none after APC (p=0.49, Fisher’s exact test).

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

<table>
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<th>p-value</th>
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<tr>
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<td>7/12 (58%)</td>
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<td>Imager</td>
<td>p-value</td>
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<td>10/12 (83%)</td>
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<td>p-value</td>
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CLINICAL STUDIES OF WIRELESS CAPSULE COLONOSCOPY

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

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-play with 4 silver-oxide batteries and a potential transmission time of 18 hours were used in 7. Lighter capsules (n=3)[SG=1.2 vs 1.7], with 2 batteries and a 2 hour rest period moving with the fluid phase were tested. 2 capsules were placed 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 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 life were tested and occasionally imaged the toilet. Clinical studies in n=13 patients revealed missed colon cancer/polyp (3), bleeding Meckel’s diverticulum (1), ulcerative colitis (2), angiodysplasia (2). Small intestinal transit times were median (4 hr), range (1.2–7.6hrs). Oro-anal transit times were 0.5–8 days. Capsules used in patients with incomplete colonoscopies provided useful clinical information. In patients selected for capsule colonoscopy management was altered in 50%.

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

Biliary/pancreas free papers

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THE POTENTIAL ROLE OF GASTRIN IN Pancreatic cancer progression-RAISED SERUM AMIDATED GASTRIN AND PROGASTRIN LEVELS IN PATIENTS WITH ADVANCED Pancreatic CANCER

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

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

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

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

GEMCITABINE DOES NOT INHIBIT THE BIOLOGICAL ACTIVITY OF A HUMAN Pancreatic TUMOUR GROWING IN THE PANCREAS OF IMMUNODEFICIENT MICE.

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Introduction: Gemcitabine (Gemzar), a novel nucleoside analogue, exerts its action by inhibiting DNA synthesis. Gemcitabine is licensed as a first line treatment for patients with locally advanced or metastatic adenocarcinoma of the pancreas and as a second line treatment of patients with 5-FU refractory pancreatic cancer (NICE guidelines 2001). The aim of this study was to assess the effect of gemcitabine on a 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 gemcitabine infusion. 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, by Western Blot of the SYBR green dye, and by Western Blotting and Zymography at the protein level.

Results: The gemcitabine treated mice had a 40% reduction in their tumour weights (p=0.045*) however there was no significant alteration in MMP gene or protein expression (p=0.1*), gastrin (p=0.48*), COX-2 (p=0.33*) and CCK2 receptor (p=0.20*) gene expression. (*Student’s t Test.)

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

MANAGEMENT OF ACUTE Pancreatitis in WALES: HOW GOOD ARE WE?

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

C. Chatzikostas1, G. Notas2, M. Roussoumoustakaki1, I. Mouzais1, I. Kofidis1, P. Skordilis3, E. Papadaki1, F. Dimoullos1, A. Thomopoulos1, D. Samanakis1, E. Vardas1, P. Antoniou1, E. Kouromitsos2, Department of Gastroenterology, University Hospital, Heraklion, Crete, Greece
Liver Research Laboratory, University of Crete Medical School, Crete, Greece

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% alcoholic-related, 7% secondary, 28% idiopathic) were studied prospectively. Data conforming to scoring systems were recorded 24 (APACHE II and III) and 48 hr (Ranson, APACHE II and III) after admission. Analysis was performed by using Hest, Pearson correlation, receiver operating characteristic (ROC) curves and area under a ROC curve (AUC).

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

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

ACUTE AND CHRONIC PANCREATITIS: DISEASES ON THE INCREASE

D.A.J. Lloyd1, A. Tinto2, A. Majeed3, R.C.N. Williamson4, J.D. Maxwell1
1St George’s Hospital; 2Office for National Statistics; 3University College; 4Hammersmith 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 Consultation Episodes’, excluding day cases, in England. Hospital admissions (HES) service from 1989/90 to 1999/00.

To investigate time trends for the numbers of hospital admissions for acute and chronic pancreatitis in England from 1989/90 to 1999/00.

Abstract 154

<table>
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<th></th>
<th>Age standardised admission rates per 100,000</th>
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<td></td>
<td>1989/90</td>
</tr>
<tr>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>17.6</td>
</tr>
<tr>
<td>% with operation</td>
<td>10</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>5.9</td>
</tr>
<tr>
<td>% with operation</td>
<td>15</td>
</tr>
</tbody>
</table>

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 Registry 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. PBAM mutation screening was undertaken for the published mutations, with sequencing in negative families. The Standardised Incidence Ratio (SIR) which is the ratio of observed PDAC to expected PDAC was calculated for histologically confirmed PDAC. Patients with at least three patients in a family with a variant of HP were included, whereas patients who under went pancreatic resection were excluded.

Results: 109 families (n=342) were recruited. 47 families (n=197; 96%) were suitable for PDAC analysis. 15 patients (BM, 7F) developed PDAC during 7648 person-years. Mean age of cancer diagnosis was 56(48-69) Yrs. Expected number of cancers was 0.21 yielding an overall SIR of 71(53-88). The SIR in males was 72(49-94) and in females was 70(47-93). The overall lifetime risk for the development of PDAC in our cohort of patients with HP was 40% [95%CI];(30–50%). The risk appeared to be minimal below the age of 40yrs, where after it increased sharply. Multivariate analysis showed that the risk of PDAC appeared to be independent of potential confounding variables.

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

AUDIT OF SECHAT TESTS: WHO TO TARGET?

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

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

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

Results: 120 patients were identified undergoing SeCHAT tests of which 51 were positive, 48 negative and 21 indeterminate (mean retention of SeCHAT at 7 days 3.75%, 33.8% and 12.4%, respectively). The indication in all cases was diarrhea. Of the 51 positive tests, 21 had previous surgery [16 terminal ileal (TI) resection, 1 stapled orchiectomy]; 21 had known TI Crohn’s disease, one had received radiotherapy involving the TI; and 2 had documented prior enteric infection. Of the negative and indeterminate tests, 4 patients had previous enteric infection, one had coeliac disease but none had known TI Crohn’s disease, previous surgery or other known predisposing factors for BAM. Prior to a positive SeCHAT test, most (90%) had
imaging of the TI compared to only 40% of those with negative tests. Of those with positive tests, 47% had a short term (3 month) response to bile acid sequestrants (BAS), but this was only sustained at 6 months in 20% of patients, the remainder being intolerant of BAS. 6 patients therefore had a diagnosis of PBAM. After 3 years of follow up, one was diagnosed with Zollinger-Ellison syndrome and another with carcinoid 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 those patients with a diagnosis of diarrhoea predominant irritable bowel syndrome.

157 IS HORMONE REPLACEMENT THERAPY ASSOCIATED WITH GALLSTONE FORMATION? A PROSPECTIVE COHORT STUDY
A.R. Hart1, R. Luben2, J. Camus1, A. Welch1, N. Wareham1, A. Welch2, N. Wareham2, S.A. Bingham3, K.T. Khaw1, N.E. Day1, 1 School of Medicine, University of East Anglia, Norwich NR4 7TJ, 2Strangeways Research Laboratories, Cambridge CB1 4RN, UK

Background: The aetiology of gallstones is unknown. High oestrogen levels, whether endogenous or through exogenous 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 yrs). 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=1.8–8.6).

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.

158 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 recognising the patients prone to recurrent gallstone related problems, it is possible to offer them early surgery, thereby reducing patient morbidity and hospital costs.

159 PLACEMENT OF BILATERAL SELF-EXPANDABLE METAL STENTS FOR COMPLEX HILAR OBSTRUCTION DUE TO CHOLANGIOCARCINOMA
S.G. Nugent, A.F. Stone, J. Gilford, M.J. Benson. Department of Gastroenterology, St. Helier Hospital, Carshalton, Surrey, UK

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

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

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

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

160 MRCP IN A DISTRICT HOSPITAL: INDICATIONS AND IMPACT ON AN ERCP SERVICE
N. Hussain, E. Breeze, P.M. Irving, D. Fowler, G.P. Bray. Department of Gastroenterology, Southend Hospital, WestCliff-on-Sea, Essex SS0 ORY, UK

MRCP was developed in 1991 and has been available in our hospital for three years. We reviewed the indications for and use of MRCP. We also assessed the effect of MRCP on ERCP usage.

116 MRCPs were done in an eight-month period in our hospital (Nov 2000 to June 2001) compared to 161 ERCPs. Annual rate of MRCP was 183 per year for a population of 350,000 (approx 1 per 2000) compared to 254 ERCPs per year (approx 1.5 per 2000). A sample of 60 MRCPs was analysed by notes and X-ray review.
FURTHER EXPERIENCE WITH SPIRAL CT
EXPERIENCE OF 5-ASA NEPHROTOXICITY IN THE

Because of the recognised complications associated with 5-ASA therapy, efforts were made to reduce the risk of nephrotoxicity. This practice should reduce the number of patients requiring ERCP, as the use of MRCP from a possible 265 to 161 (by 39%).

**Plenary session 162-166**

### 162 EXPERIENCE OF 5-ASA NEPHROTOXICITY IN THE UNITED KINGDOM

A. Jayaprakash, P.E. Stevens, S. Mian, A.S. McNerty, R.F. Logan, A.F. Muller. The Kent & Canterbury Hospital, Kent; BSG Research Unit, London; Wycombe Hospital, Bucks; University Hospital, Nottingham, UK

Nephrotoxicity is an unusual complication of 5-aminosalicylic 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.

**Results:**

- 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), Pentasa 12(2), Salofalk 1(0), & Sulphasalazine 13(8).
- The BSG reported 6 pts needing dialysis & 7 a renal transplant.

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.

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

P.J. Lamb, J. Wayman, M. Billings, M. Irving, D. Karat, N. Hayes, S.A. Raines, S.M. Griffin. Northern Oesophago-Gastric Cancer Unit at the Royal Victoria Infirmary, Newcastle upon Tyne & Cumberland Infirmary, Carlisle, UK

**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 oesophageo-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

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**Abstract 162**

<table>
<thead>
<tr>
<th>BSG</th>
<th>Renal Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>718/1298 (55.3%)</td>
</tr>
<tr>
<td>Cases &amp; age range (yr)</td>
<td>202 (15-76)</td>
</tr>
<tr>
<td>M: F sex ratio</td>
<td>106:49 (47)</td>
</tr>
<tr>
<td>Time to abnormal U&amp;E*</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>3- 12 months</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>74 (49%)</td>
</tr>
<tr>
<td>Peak serum creatinine (range umol/l)*</td>
<td>N – 900</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>N – 790</td>
</tr>
<tr>
<td>Response to stopping treatment</td>
<td>Complete</td>
</tr>
<tr>
<td>Partial</td>
<td>75 (53%)</td>
</tr>
<tr>
<td>None</td>
<td>24 (17%)</td>
</tr>
</tbody>
</table>

* Some details incomplete as some questions not answered
Reduced Pallidal Magnetisation Transfer Ratios Are Associated With Fatigue In Pre-Cirrhotic Patients With Primary Biliary Cirrhosis

D.M. Forton, M. Prince, J. Allsop, N. Patel, J. Goldblat, H.C. Thomas, M. Bassendine, D.J. Jones, S.D. Taylor-Robinson. Liver Unit, Imperial College, London; Centre for Liver Research, University of Newcastle, UK.

Fatigue is the commonest symptom in primary biliary cirrhosis (PBC), affecting individuals at all stages of the disease. We examine the hypothesis that a CNS abnormality related to cholestasis, rather than cirrhosis per se, underlies this symptom. Globus pallidus (PAL) hyper-intensity on T2-weighted MRI has been reported in biliary atresia, cirrhosis, pararental nutrition-induced cholestasis and in mangenese workers.

Methods: 18 women with PBC (14 stage I-II [mean bilirubin 11], 4 stage III-Iv [32]) and 8 age-matched healthy women underwent cerebral MRI and proton spectroscopy (H MRS). Magnetisation transfer ratios (MTR) for white matter (WM) and 4 subcortical structures were calculated and H MRS spectra (TE 135ms) were obtained from 8cm voxels in the basal ganglia (BG) and frontal WM. The patients completed the Fisk Fatigue Severity Score (FSSS) and a battery of neuropsychological tests.

Results: There were no differences between the stage I-II 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 I-Iv PBC patients (p<0.02), with no similar changes in the thalamus, putamen or caudate. The 4 stage III-Iv patients also had reduced PAL/WM ratios, although they were not statistically different from the stage 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.

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

N.I. Church, H.J. Dallal, J. Masson, A. Fraser, N.A.G. Mowat, D.A. Johnston, G. Fullarton, E. Radin, M. Turner, R. Prescott, J. Plevis, K.R. Palmer. Western General Hospital, Edinburgh; Aberdeen Royal Infirmary; Ninewells Hospital, Dundee; Gartnavel General Hospital, Glasgow; Scottish National Blood Transfusion Service; University of Edinburgh Medical School; Royal Infirmary, Edinburgh, UK.

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

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

Results: Successful primary haemostasis was achieved in 97% of both groups. Rebleeding developed in 19 (15%) of group 1 patients and 17 (15%) of group 2 patients; surgery was necessary in 16 and 13 of these respectively. Median blood transfusion (3; range 0–32 versus 2; 0–20 units) and median duration of hospital admission (5; 2–82 versus 4; 1–120 days) were similar in both groups. Adverse events occurred in 8 group 1 patients and 4 group 2 patients.

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

ERADICATION OF H. PYLORI UNLEASHES POST PPI ACID HYPERSECRETION

D. Gillen, A. Wirz, K.E.L. McColl. University Dept of Medicine & Therapeutics, Western Infirmary, Glasgow G11 6NT, UK.

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

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

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

Results: Marked rebound hypersecretion to physiological levels of gastrin was observed in the subjects who had their infection eradicated but not in those with persisting infection (table). A similar trend was seen with respect to supraphysiological gastric stimulation.

Abstract 165

Submaximal acid output (mmol/h)

<table>
<thead>
<tr>
<th>Pre-omeprazole</th>
<th>Days Post-Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 7</td>
</tr>
<tr>
<td>H. pylori eradicat</td>
<td></td>
</tr>
<tr>
<td>H. pylori not eradicat</td>
<td></td>
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</tbody>
</table>

Values are medians [quartiles], *significant versus pre at p<0.03.
**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 outpatient clinic review within 6 months of infusion.

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

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

<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 patient attendance and hospitalisation may 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.

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


Ulcerative colitis (UC) and Crohn’s disease (CD), both forms of inflammatory bowel disease (IBD) are complex traits. Intercellular adhesion molecule-1 (ICAM1) is expressed on vascular endothelium and plays a key role in the transendothelial migration of neutrophils and T-cell activation. The region harboring the ICAM1 gene on 19p13 is linked to CD in a Canadian genome wide scan, and a growing body of evidence indicates that ICAM1 could play a role in IBD development. Our previous work has replicated the Canadian linkage of 19p13 to CD. ICAM1 is known to contain at least two polymorphic sites, situated in codons 241 (R/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 fistulizing disease and 35 non-fistulizing 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 genotype by PCR-SSP for ICAM1 polymorphisms at codon R/G241 and codon K/E469. There were no differences between the groups in the frequency of R/G241. The control frequency of ICAM1 exon 6 K469 was 38.2%. In CD overall, it was 76.9% (p<0.001). For CD patients with ileal disease, the frequency was 50.9% and 43.3% for non-fistulizing disease. For patients with fistulizing disease, the K469 frequency was 69.2%, and 84.3% for non-fistulizing disease. For patients with stenosing disease, the K469 frequency was 77.4%. For UC overall, the frequency of ICAM1 exon 6 K469 was 69.7% (p<0.001). For patients with severe disease requiring colectomy, with mild total colitis, and with proctitis, the frequencies of this polymorphism were 66.22 %, 75% and 81.1% respectively. This study suggests that the alteration in the amino acid sequences of E469 to K469 of the ICAM1 molecule may influence IBD.

**RECURRENT ORAL ULCERATION (ROU) INFLAMMATORY BOWEL DISEASE (IBD): THE CLINICAL HALLMARK OF A MOLECULARLY DEFINED IBD/BEHCE'T S (BD) OVERLAP GROUP**

T. Ahmad1, K. Mulcahy-Hawes1, M. Bunce1, A. Armuzzi2, K. Welsh2, S. Marshall1, D. Jewell1. Departments of Gastroenterology, Transplant Immunology, University of Oxford; National Heart and Lung Institute, Imperial College, London, UK

**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 DRB1*0103 (16.5% ROU+ vs 3.8% ROU; P=0.0003; 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 fulfilled the criteria for diagnosis of BD. 4. In our IBD clinic 5% of patients clinically and molecularly resemble BD.

**LYMPHOCYTE TELOMERASE EXPRESSION IN INFLAMMATORY BOWEL DISEASE**


**Background:** Telomerase knockout mice develop ulceration and atrophy of the bowel. In humans colonic telomerase activity is decreased in ulcerative colitis but it is unknown whether this is restricted to the colon. The object of this study was to assess lymphocyte telomerase enzyme activity in patients with inflammatory bowel disease and to determine the role of the mRNA that encodes its catalytic subunit (hTERT) in the regulation of enzyme activity.
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) p < 0.001 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: Telomerase telomere 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 hypervariable, non-coding control region known as the D-Loop. A number of recent investigations have revealed that a proportion of colorectal adenocarcinomas harbour mtDNA mutations, not present in normal surrounding mucosa and are classified as tumour-specific. Tumour specific mtDNA mutations have also been observed in many other tumours including lung and bladder and it has been suggested that these mutations may serve as diagnostic markers for cancer. The D-Loop, used commonly in population studies and the most mutable region within mtDNA, may be rapidly and cost-effectively scanned for mutations. Previous studies involving the search for tumour-specific mtDNA mutations in colorectal cancer have relied on small sample sizes or have failed to reveal mutations within the D-Loop. Using PCR-SSCP and DNA sequencing we have undertaken a comprehensive survey of the D-Loop in adenocarcinoma and normal mucosa of twenty patients. Results: (i) 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, 25% 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 63 and 52 and one T:A/A:T transversion at nucleotide position 69.

Nontumour adjacent colorectal adenocarcinomas, 25% showed tumour-specific mutations which were 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. Results: (i) 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, 25% 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 63 and 52 and one T:A/A:T transversion at nucleotide position 69.

Discussion: There has been one study examining serial HCV specific CD4+ responses during treatment with pegylated interferon-α and ribavirin, correlating with viral response. However, recent data from a large international trial suggests that interferon treatment plus ribavirin achieves a sustained virological response in around 40% of those treated. The addition of an antiviral drug to interferon-α therapy 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. Our study suggests that HCV specific responses are present in patients with chronic hepatitis C, and that interferon treatment improves these responses. Our study correlated with virological response.

TUMOUR-ASSOCIATED GENETIC CHANGES DURING TREATMENT WITH PEGYLATED INTERFERON-α AND RIBAVIRIN CORRELATE WITH VIRAL RESPONSE
C.L. Brooks, E.A. Sanders, S. Hadfield, S. Green, W.M. Rosenberg.

Introduction: Hepatitis C virus (HCV) establishes a chronic infection in up to 85% of those exposed. The resultant immune mediated hepatic injury 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 an antiviral drug to interferon-α therapy 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. Our study aimed to characterise HCV specific responses in CHC patients at the start of treatment with pegylated 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 positive and negative controls. Cellular proliferation was assessed by incorporation of tritiated thymidine. Cellular markers of activation and cytokine secretion were assayed by fluorescence activated cell scanning. The assays were repeated at regular intervals throughout treatment and follow up. At each time point, viral load was measured by PCR and viral responses were considered when viral load was less than 400 IU/ml.

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 during treatment with pegylated interferon, ribavirin and interferon therapy in patients with chronic hepatitis C. Our study has similar results and we have shown 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 APOPTOSIS IN HELICOBACTER PYLORI INFECTED MONGOLIAN GERBILS
M. Court, M.A. Aboshkiwa, M.F. Dixon, P.A. Robinson, J.E. Crabtree.
Molecular Medicine Unit, St James’s Hospital, Leeds LS9 7TF, UK

Introduction: Chronic H. pylori infection in Mongolian gerbils (MG) has been demonstrated to result in gastric cancer. The aims of this study were to assess the ability of the mouse adapted SS1 strain to...
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 immunohistochemically and by TUNEL assay. Infection was confirmed histologically and by culture. Strains were identified as SS1 by RAPD-PCR and sequence analysis of glmM.

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 4, 12 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 gastropathy 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


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 gastric mucosa in neonatal 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, CHAPTER 2.1 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 10⁻¹⁰ 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 sensitive cells than somatic tissue but like somatic neurons responses are enhanced at reduced pH.

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

L.A. Haughton1, W. Atkinson1, P. Whitaker2, P.J. Whorwell1, M. 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 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 (443.9ng/ml/10⁶ platelets, adjusted geometric mean) than healthy female controls (342.86ng/ml/10⁶ 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.

Abstract 176, Figure 1

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 natural ligands for the galectins but galectin-3 expression is implicated in tumour invasion and metastasis. We have therefore investigated the possible ligand(s) for recombinant galectin-3 in HT-29 colon cancer cells.

Methods and Results: HT-29 cells were grown to 70% confluence, harvested, and a cytoplasmic extract prepared. The extract was then incubated with increasing concentrations of MUC-1 and MUC-2 in the presence of recombinant galectin-3.

Results: The level of binding between MUC-1 and galectin-3 increased with increasing concentrations of MUC-1 and was specific to MUC-1 since no binding was observed with MUC-2.

Conclusion: MUC-1 is a novel ligand for galectin-3 and is up-regulated in invasive HT-29 colorectal cancer cells.
180 BONE MINERAL DENSITY AND MINERAL STATUS OF ILEOSTOMY PATIENTS

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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 of Ca and Mg were made in all patients 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). There was no significant difference between the two groups in menopausal status or duration of ileostomy. The two protein bands observed for MUC-1 were due to the two different alleles of MUC-1. HT-29 cells were separated into invasive and non-invasive cell types by their ability to migrate through a 0.5mm Matrigel. The technique employed was a Membrane Invasion Culture System (MICS). Immuno-confocal microscopy of invasive HT-29 cells showed co-localisation of MUC-1 and galecin-3 whereas MUC-1 expression was weak in the non-invasive cells.

Conclusions: The transmembrane TF expressing mucin MUC-1 is a natural ligand for galecin-3. Its increased expression is correlated with a more invasive phenotype in colon cancer cells.

179 HFE AND TF2 INTERACT IN SMALL-INTESTINAL CRYPT CELLS: A MECHANISM FOR IRON HOMEOSTASIS IN HEREDITARY HAEMOCHROMATOSIS

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Transferrin receptor 2 (TR2) is a recently-identified homologue of the ubiquitous transferrin receptor (TR) and is expressed in the liver and small intestine. Mutations in the HFE gene predispose to hereditary haemochromatosis and a role for HFE in the signalling of body iron status within small-intestinal crypt cells has been proposed. TR2 mutated however account for rare forms of non-HFE related haemochromatosis suggesting a key role for this receptor sub-class in the control of intestinal iron absorption.

To investigate cellular interactions of HFE and TR2 a panel of rabbit and avian polyclonal antisera was generated to specific peptide sequences of the human and mouse proteins. Antibodies were first characterized by Western immunoblotting. Using laser confocal microscopy in mouse and human duodenal sections, strong staining of TR2 was observed in the crypts, where colocalisation occurred with HFE; no staining of HFE and TR2 was observed in villus enterocytes. In contrast TR expression, examined using a commercial murine antibody, was ubiquitous but did not colocalise with HFE. The localisation of HFE and TR2 was further examined in situ in human Caco-2 cells, which have a small intestinal phenotype. Using confocal microscopy TR2 stained abundantly with a vesicular pattern in undifferentiated Caco-2 cells. No colocalisation with TR was observed by dual-label fluorescence studies confirming the specificity of the TR2 antibody. HFE colocalised with TR2 in an endosomal compartment following addition of ion-saturated transferrin to the culture medium.

Identification of TR2 in small-intestinal crypt cells and the known effect of disabling mutations in the cognate gene would support a key regulatory role for this receptor in intestinal iron absorption. Colocalisation of endogenous TR2 and HFE suggests functional coupling in an endosomal transport pathway for crypt cell iron signalling.

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181 BEDSIDE INSERTION OF NASOJEJUNAL FEEDING TUBE: BENMARK IS BEST

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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 Medicina (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 metoclopromide (10mg) was given prior to insertion guidance by the same person (CWYL) for pre- and / or postoperative feeding. Bolus IV metoclopromide (10mg) was given prior to insertion.

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 was achieved significantly more frequently 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 PEPITIC ULCER DISEASE (PUD) TREATED WITH ENDOCOPIC 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. None 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.

ENDOSCOPIC PALLIATIVE TREATMENT IN OESOPHAGEAL AND GASTRIC CANCER: EVIDENCE FROM 948 PATIENTS IN THE POPULATION BASED SCOTTISH AUDIT

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The population based Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) accrued data over a 2 year period on 3,293 patients of whom 948, predominantly with oesophageal or junctional cancer, received endoscopic palliative treatment (EPT). Of these placement alone (506 patients) or LASER treatment alone (117 patients) were popular, but combination approaches supported by radiotherapy (188 patients) or chemotherapy (134 patients) were also administered. There was significant variation in delivery of EPT by health board of residence (chi square test, P<0.001), but not by deprivation quintile.

Complications were recorded in 221/948 patients (23%) and were associated with multiple treatments (P<0.001). Oesophageal perforation was uncommon and occurred in 23 patients post stent and 3 patients after LASER.

Stent alone was used for the relief of grade 3 or 4 dysphagia, stent and radiotherapy for grades 2,3,4 and LASER for grades 1,2,3. The majority of patients (>65%) had normal physical activity or only strenuous activity restricted, but before undergoing EPT. Stents were deemed by the consultant looking after the patient to have been used appropriately for 95% of patients and LASER for 83% of patients.

Survival for all the patients receiving EPT was 40% at 6 months, 17% at 12 months 10% at 18 months and 6% at 24 months, suggesting no benefits from EPT intervention in patients with advanced disease.

While there may be differences between the symptoms and staging of patients receiving different types of EPT, there is evidence for regional variations in the approaches used. However, appropriate use of intervention may provide good palliation for all several months.
CURRENT ISSUES IN THE MANAGEMENT OF COLONIC POLyps: A RETROSPECTIVE REVIEW OF 2806 CONSECUTIVE POLYPECTOMIES

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Background: Based on current knowledge, population screening and the removal of colon adenomas would be an effective means of reducing the incidence of colorectal cancer. However, a sound understanding of the distribution of adenomas and risks of polyectomy is a prerequisite to implementation, and will assist in the selection of the optimal screening modality and the safest and most effective methods for post-polypectomy. We therefore studied endoscopy and polyectomy 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 55, neoplasia surveillance 387, polyposis 55, IBD 37, not recorded 9) who had undergone 1023 consecutive colonoscopies with polypectomy during a 22-month period, were examined retrospectively. Complications were identified using a postal questionnaire.

Results: 2806 polypectomies were performed, 37.9% by hot-biopsy, 30.6% by snare and 23.3% by Argon Plasma Coagulation (APC). 44.7% were benign adenomas and 47.8% of these (excluding polyposis) were located proximal to the splenic flexure. 27% of advanced adenomas (size >1cm or villous histology) were proximal. Polypectomy failed to yield a specimen for analysis in 19.3% of 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 is less than previously reported which may reflect improved technique. Hot biopsy and APC both appear to be safe for the removal of small polyps, but snare techniques, although safe, frequently fail to yield tissue for histology. No increase in secondary haemorrhage was seen in patients taking aspirin.

VIDEO-ASSESSMENT OF COLONOSCOPY WITHDRAWAL TECHNIQUE

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Background: Colonoscopy withdrawal technique has been shown to be important in the detection of adenomas. We aimed to survey current practice in a single UK endoscopy department, as well as assessing the effect of video recording on examination quality.

Method: With ethics committee approval and patient consent, consecutive routine colonoscopy exubations were video recorded using a remote, closed-circuit TV system. Endoscopists were informed that recording would take place when a “recording-light”, conspicuously placed in the endoscopy room, was illuminated. However recording took place continuously. Exubation lists were randomly assigned to “open” or “blind” recording. The video footage was reviewed by a blinded panel of 3 experienced colonoscopists. Exubations were scored by consensus for seven segments of the colon using 5 parameters (looking behind folds, cleaning pools, adequacy of distraction, 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, with an effective means of cancer. 52.7% exubations attained a mean score of less than 30 (an arbitrary minimum score for acceptable quality). There was no difference in exubation scores or time with blinded compared with open video recording (see table). There was also no difference between groups in performance of retroflexion in the rectum (12% overall) of the detection of adenomas (p=0.24).

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

GENETIC THROMBOPHILIA AND PERI-PARTUM LIVER FAILURE

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Introduction: The aetiology of severe pregnancy-related disorders remains poorly characterised. One hypothesis is that the clinical disorders recognised - Acute Fatty Liver of Pregnancy [AFLP], HELLP syndrome and Veno-occlusive disease - represent microangiopathic disorders. Thrombophilic disorders have previously been implicated in serious hypertensive complications of pregnancy where microangiopathy is evident. Accordingly, we tested the hypothesis that a higher incidence of genetic thrombophilia would be present in this population.

Methods: Twenty-eight patients with a history of peri-partum liver failure were tested [AFLP 22, HELLP syndrome 3, and Veno-occlusive disease 3. Median age 30 years (range 21–36). Twenty-eight patients were Caucasian and five Afro-Caribbean. All presented in the third trimester. Only one patient had a known pre-existing pro-thrombotic disorder. All patients had thrombophilia screens performed post-partum once fully recovered from their illness (factor V leiden [FVL] and prothrombin G20210A gene mutations, anti-cardiolipin antibody and lupus anti-coagulant, anti-thrombin III and protein C and S levels).

Results: A pro-thrombotic disorder was present in 12/28 (43%) patients. FVL heterozygosity was present in 5/23 Caucasian patients (17.5%). GT G20210A gene heterozygosity was present in 2/28 (7%). Anti-cardiolipin antibody was detected in 4/28 (14%). Lupus anti-coagulant was detected in 1 patient with AFLP. In the patients where a diagnosis of AFLP was made, genetic thrombophilia was present in 10/23 (42%). Protein C and S deficiency was not detected in patient.

Conclusion: The above results lend some support to the hypothesis that microvascular thrombosis may play a pathogenic role in a subgroup of patients with peri-partum liver failure. However further predisposing factors for these serious disorders require to be elucidated.

NEUROLOGICAL AND COGNITIVE DYSFUNCTION IN “NEVER-ENCEPHALOPATHIC” PATIENTS WAITING LIVER TRANSPLANTATION

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Introduction: Patients with liver failure who are not clinically encephalopathic can show evidence of neuropsychological impairment. Inadequate treatment of previous hepatic encephalopathy is often blamed. Repeated episodes of hepatic encephalopathy may play a pathogenic role in a subgroup of patients with peri-partum liver failure. However further predisposing factors for these serious disorders require to be elucidated.
were no significant differences between baseline characteristics of patients and controls. Highly significant global impairment of cognitive function was detected, with memory and visuo-spatial problems being prominent. No abnormalities were detected with the commonly used trailmaking test. Twelve patients had an abnormal neurological examination displaying many of the physical signs associated with ADHC.

Discussion: Cognitive and neurological dysfunction occurs in patients with end stage liver failure in the absence of previous HE. It is unlikely that the progressive neurological and cognitive decline that can occur in these patients is due to repeated episodes of HE. The impairment that occurs is severe, and affects many aspects of cognitive function. This has implications for the pre-operative counselling of these patients and for obtaining informed consent. Current methods of monitoring cognitive impairment clinically, such as trailmaking tests, may be inadequate.

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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Materials/Method: 69% and 72% specific respectively, as subjects with fibrosis showed earlier arrival times than comparative untreated subjects. 10 interferon-treated patients showed AT<24s and CDT<10s was 100% sensitive for cirrhosis but only 4.9 respectively (Kruskal Wallis ANOVA, p<0.001).

Results: An AT<24s and CDT<10s was 100% sensitive for cirrhosis but only 4.5 and 36.8s ± 4.5 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 earlier arrival times than comparative untreated subjects. 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.

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 5hourly 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 those substrates at any time point sampled. Animals who received paracetamol showed significant increases in the concentrations of lactate, pyruvate and the amino acids. Increase of lactate became significant at 1.5 hours and at 2.5 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.

GENETIC INFLUENCES IN GASTRO-OESOPHAGEAL REFLUX DISEASE: A TWIN STUDY

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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.

HEARTBURN IN PATIENTS WITH UNTREATED ACHALASIA

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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 gastrooesophageal reflux disease (GORD).

Methods: We studied the medical notes of all patients diagnosed with achalasia in our laboratory over the past 10 years, and
PLASMA LEPTIN BEFORE AND AFTER CURE OF PANCREATIC STELLATE CELLS EXPRESS LOW AFFINITY RECEPTORS AND SHOULD BE INVESTIGATED WITH A 24-HOUR pH STUDY.

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%) were classified as vigorous 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.

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.

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 acid reflux, Barrett’s and oesophago-gastral 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 studied by the Wilcoxon rank sum test. Paired comparison was made using the trapezoid rule. Paired comparison was used to test for significant change in plasma leptin following cure of H. pylori.

Results: Before H. pylori cure, median 6 hour integrated plasma leptin was 23.66 mcg/L (7.33 – 128.22), and after cure it was 26.75 mcg/L (7.43–72.81). Paired comparison was made by the Wilcoxon rank sum test.

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.

PARADOXICAL DUAL EFFECT OF HELICOBACTER PYLORI ERADICATION THERAPY ON HEARTBURN AND ACID REFLUX: THE BRISTOL HELICOBACTER PROJECT

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Helicobacter pylori eradication therapy has been reported in some studies to result in increased heartburn and acid reflux. However, other studies show either no effect on these symptoms, or even a beneficial effect. We have investigated these contradictory findings, as part of the community-based Bristol Helicobacter Project.

Methods: 10,537 people aged 20–59 years gave informed consent to take part in the Bristol Helicobacter Project, a community-based prospective randomised controlled trial of the effects of 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. 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. Subsets where the most marked 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.

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 cholangiocarcinocyte 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 nucleas P1 method of “P-postlabelling. Relative adduct labelling values (RAL, adducts/10^9 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.

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. PAS stained.
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 was 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±11% and 30±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 choledocholithotomy). 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 biliary drainage as definitive treatment for patients at high surgical risk.

Biliary and pancreas posters

P. Dunckley, A.S. Mee. Department of Gastroenterology, The Royal Berkshire Hospital, London Road, Reading, Berkshire, UK

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 represent 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 been represented 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 24 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 ENDOSCOPIC RETROGRADE BILIARY BRUSH CYTOLOGY

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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 polymorphonuclear exudates, thus improving cytomorphology and diagnostic accuracy.

Objectives: [1] To compare the performance of endoscopic retrograde biliary brush cytology (ERBC) prepared by Thin Prep® 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.

Abstract 199

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>Positive yield of total malignant</td>
<td>9/12</td>
<td>7/9</td>
<td>1/5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75%</td>
<td>77%</td>
<td>20%</td>
</tr>
</tbody>
</table>

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

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Background: Studies in other countries have suggested that the overall cholecystectomy rate increased following the introduction of the laparoscopic technique in 1985.
Objective: The aim of this study was to evaluate changes in rates of laparoscopic cholecystectomy (LC) in Ireland, over a 7 year period. We also performed a subset analysis in our 630 bed teaching hospital to determine characteristics of patients, imaging modalities used and indications for surgery.

Methods: Data for cholecystectomies performed in Ireland, in 60 Irish public hospitals, were obtained from the Hospital In Patient Episode Scheme, based at the Economic and Social Research Institute (ESRI). The information for the subset analysis in our hospital was retrieved from 139 patient chart reviews, comparing two six month periods, in 1996 and 2000.

Results: Overall, the rate for total cholecystectomies in Ireland (laparoscopic and open), rose by 17% over the 7 year study period. LC rates rose by 45%, with the largest increase of 15.4% observed in the 0–19 year 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 (0.5%), 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.

201 PRIORITISING PATIENTS FOR CHOLECYSTECTOMY

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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 ADDRESSING CELL ADHESION MOLECULE-1 (MADCAM-1) AND PODODPLANIN LOCATION IN PRIMARY SCLEROSING CHOLANGITIS (PSC) & PRIMARY BILIARY CIRRHOSIS (PBC)

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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 connective tissue sections, localized to the 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.

Conclusions: MadCAM-1 expression demonstrated within lymphoid aggregates and in PBP vessels identifies presumptive sites of lymphocyte emigration. We have demonstrated MadCAM-1 immunoreactivity 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-HEREDITARY CHRONIC PANCREATITIS: A CASUALTY OF XENOBIOTIC STRESS

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Epidemiological studies have demonstrated a variety of potential environmental and cellular stress related factors that may alter susceptibility to chronic pancreatitis (CP), however a direct causal and mechanistic role has not been established. Impaired detoxification of environmental pollutants may overwhelm cellular oxidative defences leading to lipid membrane damage, protein denaturation and DNA adduct formation.

The aim of this study was to determine the relationship between functional genetic polymorphisms in the antioxidant / xenobiotic metabolising enzymes, glutathione-s transferases (GST-M1, GST-T1, GST-P1), 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 40H), and 206 age and sex matched controls were recruited. The prevalence of the GST-T1 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-alcoholic related disease (p<0.03). In contrast to the data with GST-T1, no significant associations were observed between GST-P1, GST-M1, and MnSOD genotypes and susceptibility to CP.
The GSTT-1 functional genotype is associated with an increased susceptibility to CP, whether this is attributable to its phase-II conjugation or anti-oxidant properties remains to be determined.

THE GENETIC PRE-DISPOSITION TO SEVERE PANCREATITIS IS ASSOCIATED WITH DISTURBANCES IN GLUTATHIONE REGULATION


Disturbances in glutathione regulation appear central to the pathogenesis of severe acute pancreatitis (AP), by altering cellular integrity and impairing anti-oxidant defences. Individual differences 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 Ala/Val1 bi-allelic 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) T-1*A gene associated with severe disease (OR 4.8), and for potential influences on glutathione disturbance (glutathione and transulfuration pathway).

In total, 320 patients with AP (90 severe) and 206 matched healthy controls were recruited. Severity of AP was assessed using the Atlanta criteria, and serial venous blood samples were taken at 24-hour intervals (from pain onset) for C-reactive protein (CRP), γ-glutamyl transpeptidase (γGT), alkaline phosphatase (ALP), and alanine transferase (ALT).

A severe attack of AP was associated with an early persistent systemic ALT and γ-GT levels (p=0.03) compared to the wild type MnSOD (p=0.01). Although MnSOD polymorphism was not independently associated with severity of AP, among patients of the functional GSTT-1*A genotype the polymorphic MnSOD (AA) genotype was associated with a significantly greater peak CRP (p=0.02), but significantly lower systemic ALT and γ-GT levels (p=0.03) compared to the wild type MnSOD (p=0.01).

Susceptibility to severe inflammatory stress may in part be mediated by differences in the ability to efficiently detoxify reactive oxygen species, through a profound depletion of cellular glutathione as a consequence of altered hepatic function.

DISTURBANCE OF GLUTATHIONE REGULATION IN SEVERE ACUTE GALLSTONE PANCREATITIS


Impairment in hepatocellular function often accompanies the severe systemic inflammatory response and multi-organ failure observed in acute pancreatitis (AP). These disturbances may contribute to the inability of the liver to replenish glutathione levels, the depletion of which has been demonstrated to increase cellular susceptibility to inflammatory stress. We therefore sought to determine if severe AP is associated with down-regulation of glutathione metabolism by observing the profile of ALT (transulfuration pathway) and γ-glutamyl transpeptidase 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, 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.

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 pancreatoduodenectomy 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, texture and edge 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 images 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 within 9 of 19 tumours to be detected.

FROM GP REFERRAL TO DEFINITIVE TREATMENT: A BREAKDOWN OF DELAYS IN THE MANAGEMENT OF PATIENTS WITH PANCREATOBILIARY TUMOURS

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The aim of this study was to assess the extent of delays at different stages in the management of patients with pancreatobiliary tumours, from GP referral to definitive treatment at a District General Hospital (DGH) or Hepato-Pancreato-Biliary (HPB) Unit.

The note of patients with pancreatobiliary malignancy diagnosed at a DGH over a 2 year period (1/9/99 to 1/9/01) were reviewed. Mode of referral, presenting symptoms, investigations performed and treatment were recorded. The time taken at various stages in assessment and treatment was noted, as was delay waiting for investigations.

Of the 42 patients identified, 27 presented with jaundice. 24 were seen in the clinic, 16 were acute GP admissions and 2 were A&E referrals. 7 were referred on to the HPB Unit (see table). Unacceptable delays occurred in those patients referred to the HPB Unit. If assessment of the majority of patients is to be carried out at HPB Units these waiting times will need to be shortened to conform to National Cancer Plan targets.
A PROSPECTIVE STUDY OF THE PABA TEST AND PAIN COPING STRATEGIES AND QUALITY OF LIFE IN TREATMENT OF FAECAL INCONTINENCE DUE TO PANCREATIC DISEASE

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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 treated with initial temporary and subsequent permanent stimulation. The median pre-operative episodes of faecal incontinence per week was 15 (7–25). The median pre-operative duration of incontinence was 5 years (5–9) and of scleroderma 13 years (4–29). All had failed traditional treatment including anti-diarrhoeal agents and behavioural therapy (biofeedback). A three-week bowel habit diary, quality of life assessment (SF36), endoanal ultrasound and 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) mmHg). Rectal sensation to distension improved at threshold volume (53 [17] ml air v 33 [20]), urge volume (83 [18] v 58 [23]) and maximum tolerated volume [143 [23] v 75 [34]]. There were no major complications.

Conclusion: Sacral nerve stimulation is a safe and very effective treatment for faecal incontinence in patients suffering with scleroderma when other treatments have failed.

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


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?

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Materials and Methods: Admission rates for colonic diverticulitis (ICD9: 562.1, ICD10: K57.2–57.9), excluding day cases but including diverticular abscess and perforation, operation and case fatality rates were obtained from Department of Health Hospital Episode Statistics.

Results: There has been a steady increase in age-standardised hospital admission rates for both sexes and in all age groups over the study period. Admission rates increased with age for both sexes. The percentage of hospital admissions with an operation has also risen for both males and females. There has been no significant change in case fatality rates over this time for either sex [see table].

Abstract 212

<table>
<thead>
<tr>
<th>Colonic diverticulitis</th>
<th>1989/90</th>
<th>1999-2000</th>
<th>% change</th>
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<tbody>
<tr>
<td>Males/Females</td>
<td>M/F/M/F</td>
<td>M/F/M/F</td>
<td>M/F/M/F</td>
</tr>
<tr>
<td>Admission rate/ 100,000 population</td>
<td>20.1/28.6</td>
<td>23.2/31.9</td>
<td>16/12</td>
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<tr>
<td>% of admissions with operation</td>
<td>22.9/20</td>
<td>27/22</td>
<td>14</td>
</tr>
<tr>
<td>Case fatality rate %</td>
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<td>3.2</td>
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</table>

Conclusions: The hospital admission rates for colonic diverticulitis has increased from 1989/90 to 1999/00. As the proportion of patients who had surgical operations has also increased, while case fatality rates have remained much the same, the rise in admission rates may be due to a true increase in the incidence of colonic diverticulitis. With an aging population, colonic diverticulitis is likely be an increasing health problem in England.

213 THE RELATIONSHIP BETWEEN CYCLOOXYGENASE-2 EXPRESSION AND MICROVESSEL DENSITY IN COLORECTAL CANCER

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Introduction: Cyclooxygenase 2 (COX-2) is up regulated in colorectal carcinomas and related to survival, lymph node and distant metastases. The exact role of COX-2 in colorectal cancer, in particular with regard to angiogenesis and tumour vascular development, is yet to be delineated. Our group have shown that VEGF mediates endothelial cell proliferation via COX and that adhesion of endothelial cells to the extracellular matrix via integrins induces COX-2. The aim of this study was to examine the relationship between tumour cell expression of COX-2 and vessel formation within tumour by microvesSEL density (MVD) in colorectal cancer.

Methods: Seventy patients for whom full clinical and pathological data 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 (Caymar) and an endothelial cell antibody, CD-34 (clone GBehD10) Dako) were used on formalin fixed 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 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

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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. Study 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), diverticulitis (7)] 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, 10 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%, 2: 1–5%, 3: 6–10%, 4: >10%.

Results: A single cytokeratin positive epithelial cell was identified in 1 (1%) of the lymph nodes in the levels immunostained with AE1/
AE1/AE3 and Cam 5.2. This cell could not be identified in the level stained with pan-cytokeratin. No cytokeratin positive epithelial cell was present in any of the other lymph nodes with all 3 antibodies. Rare to 2+ cytokeratin immunoreactive dendritic histiocytes were observed in 50% of lymph nodes with MNF 119 and in 14% with Cam 5.2. With AE1/AE3, no immunoreactive dendritic histiocytes were seen in any of the cases.

Conclusion: Isolated cytokeratin positive epithelial cells are rare in benign pericolic lymph nodes. Cytokeratin positive epithelial cells in lymph nodes draining a carcinoma could represent either tumor cells or histiocytic cells which have adsorbed cytokeratin antigen shed by tumor cells. AE1/AE3 is more specific than Cam 5.2 and pan-cytokeratin in the identification of epithelial cells in lymph nodes.

215 INTER-EXAMINER REPRODUCIBILITY OF ANORECTAL MOTOR AND SENSORY FUNCTION TESTS

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Background: Anorectal physiological tests are used to influence management of benign anorectal disorders. However their inter-examiner reproducibility has not been well established. We assessed statistical reproducibility and reproducibility with respect to clinical significance.

Methods: 37 consecutive patients referred for routine anorectal physiological testing were studied by two investigators, unaware of the other’s results, in random order, 30 minutes apart. Maximum anal canal resting (MRP), squeeze (SP) and involuntary contraction pressures (CP, pressure generated on coughing) were assessed using a water perfused manometry system; anal canal (AS) and rectal pressures (RS) were assessed using an 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 of both investigators for each of the described tests, after a log transformation. (ii) Reproducibility with respect to clinical result (how often result was consistently within or outside the normal range) was also assessed.

Results: (i) For all the measured variables the largest differences between observers were found when the means were greater, which demonstrates that the data from the two investigators were in statistical agreement, and suited to log transformation. All measured parameters, apart from CP, were significantly reproducible. (ii) The percentage of inter-examiner results showing consistency in relation to a normal or abnormal outcome (within or without 2SD of normal mean) were: MRP 92%, SP 78%, CP 62%, AS 84%, RS 95%.

Conclusions: All tests, apart from CP were statistically reproducible. Therefore when these tests are performed using the same standardised technique one can have confidence in the numerical accuracy of the results. These tests are also usually consistent in producing a result which is abnormal, and therefore of particular clinical significance. CP provides only a rough guide to pelvic floor contraction, but is not a precise measurement. It may be best used as present or absent above a certain level.

216 HYPNOTHERAPY FOR IRRITABLE BOWEL SYNDROME: IMPROVEMENT IS LONG-LASTING AND REDUCES HEALTHCARE COSTS

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Background: We have shown that hypnototherapy (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 hypnototherapy, medication use and consultation rates.

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% consular 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 a pre-HT (pre-HT v post-HT v follow-up, median [IQR]: pain severity: 54(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 23(20.50); bowel habit dissatisfaction: 74(58.97) v 35(27.52) v 38(33.66); life interference: 75(68.89) v 33(22.60) v 39(30.65); forming an overall score: 232(182.97) v 156(91.249) v 17(118,268). Extra-colonic symptoms, QOL and HAD scores all also remained improved (all p<0.001).

Conclusion: This study confirms the long-term benefit of HT. In addition, the substantial reduction of medication and consultation rates highlights the significant economic advantages of this form of treatment.

217 A PROSPECTIVE RANDOMISED CONTROLLED TRIAL OF CONSERVATIVE MANAGEMENT VERSUS OPERATION IN PROLAPSED THROMBOSED HAEMORRHOIDS

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Introduction: Conservative management has been the mainstay of treatment of prolapsed thrombosed haemorrhoids (PTH). The aim of our study was to evaluate the role of operative management for PTH in a randomised trial

Methods: Fifty consecutive patients (male - 43 years; mean 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, duration of hospital stay was less in those receiving operation. Even though there was a tendency towards a higher rate of urinary retention and bleeding after operation it was not statistically significant. We recommend haemorrhoidectomy as the treatment of choice for prolapsed thrombosed haemorrhoids.

218 ELECTIVE COLECTOMY FOR DIVERTICULAR DISEASE?

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Introduction: Colonic diverticular disease is a common problem in the Western world. Studies about the natural history of diverticular disease and the incidence of complications after an initial attack have reported varying outcomes. This has led to a debate on the value of elective colectomy in preventing complications of diverticular disease.

Aim: To assess whether the complications of diverticular disease requiring emergency or urgent surgical intervention are related to previous episodes of diverticulitis and if elective colectomy might prevent such complications.

Methods and Materials: A retrospective analysis was performed on all the patients who were admitted with complicated diverticular disease in two adjacent district general hospitals between 1993-2000 and information was recorded on the past history of these patients with regard to previous investigations or treatment for diverticular disease.

Results: A total number of 108 patients (42 males and 66 females) were admitted with complicated diverticular disease. Ninety eight
patients (91%) were emergency admissions and 10 patients (9%) were urgent admissions. Ninety eight patients (91%) underwent a Hartmann’s procedure. Two patients had a subtotal colectomy and 4 patients had a sigmoid colectomy with primary anastomosis. Four patients were not operated on due to their poor general condition. Out of the 108 patients, only 26 patients (24%) 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 in patients with known diverticular disease to identify any further risk factors for development of future complications. This would help to identify a group of patients who may benefit from elective colectomy.

219 GASTROINTESTINAL SYMPTOMS AFTER RADIOTHERAPY FOR PELVIC CANCER

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Introduction: About 13,000 patients undergo pelvic radiotherapy annually in the UK. The incidence of severe GI toxicity (fistulation, bowel obstruction, transfusion dependent bleeding or secondary cancer) is not known but probably occurs in 4–8% at 5 years. More common are symptoms such as incontinence or diarrhoea which may significantly impair quality of life in >50% of long term survivors. Aim: To describe the symptoms and outcomes of patients following pelvic radiotherapy referred to a specialist gastroenterology/GI oncology clinic during its first year.

Methods: Oncologists were offered direct flexible sigmoidoscopy for any patient with bright rectal bleeding without other symptoms, irrespective of proctoscopic findings. Other patients were reviewed in clinic. Data were recorded prospectively.

Results: Over 12 months, 60 patients were referred: 37 men, 23 women with a median age 64 years (range 38–80). Primary tumours sites included prostate (n=33), cervix (n=12), endometrium (n=7), bladder (n=3), large bowel (n=2), and anus, vagina and ovary (n=1 each). Radiotherapy was given a median 2 range 0.5–21 years previously except in 3 patients referred to exclude inflammatory bowel disease before starting treatment. Major symptoms included rectal bleeding (n=27), frequency (n=22), faecal incontinence (n=19), diarrhoea (n=14), pain (n=8), steatorrhoea (n=5), subacute obstruction (n=4) and tenesmus (n=3). Eight patients described significantly abnormal bowel habit before starting radiotherapy. Of patients with bleeding alone (n=19), 1 had no radiation proctitis but was bleeding from mucosal prolapse, 3 had unsuspected advanced adenomas and 2 had squamous polyps. Sucralfate 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 pancreatic insufficiency, 2 fatty acid malabsorption). Pain was associated with relapse in 50%. Two patients with obstruction required surgery.

Conclusions: Chronic GI symptoms after radiotherapy are often highly debilitating and complex to assess, but may respond dramatically to simple combination therapies. Patients with new onset rectal bleeding following radiotherapy should be offered at least a flexible sigmoidoscopy. Patients appear to benefit from being seen in a specialist setting.

220 TIMING OF OPERATION AFTER RADIOTHERAPY FOR RECTAL CANCER

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Aim: Preoperative adjuvant radiotherapy for rectal cancer has two problems, radio sensitivity and timing of operation. We have examined the effect of radiation and its timing on the relationship between apoptotic cell index (AI) and proliferative activity index (PI).

Methods: Patients were given one of three alternative modalities, standard radiotherapy (SD) [40Gy, fractionation of 4-8 weeks, n=23], short-course radiotherapy (SC) [25Gy, 1-2 weeks, n=11], or chemoradiotherapy (CR) [45Gy, 6-9 weeks, n=7]. AI and PI were estimated in paired sections of biopsies and post-irradiated resected tumours. The radiation ratio was histologically estimated and radio sensitive 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 CR, respectively. In SD, the AI was significantly higher (5.9 vs 2.7; p= 0.001) and the PI was significantly lower (33.9 vs 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 vs 46, p=0.005]. However, the AI of radioresistant subgroup was lower than that of resistant one [2.4 vs 4.2; p=0.005]. Plotting each AI according to time course from finishing radiotherapy to operation in SD showed that the slope of the radiosensitive subgroup was steeper than in the radioresistant one and extrapolation back to the end of radiotherapy (day 0), suggests that in the radioresistant subgroup would have a high AI. The difference between two slopes means that in radioresistant 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; radio sensitive tumours should be surgically resected earlier than the more resistant ones.

221 RANDOMISED CONTROLLED TRIAL OF BIOFEEDBACK FOR FAECAL INCONTINENCE

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Background: Behavioural treatment (biofeedback) has been reported to improve symptoms in a majority of patients with faecal incontinence, but there are no trials comparing biofeedback with placebo or standard medical care.

Methods: 171 consecutive patients with faecal incontinence to solid or liquid stool were assessed by anal ultrasound and then stratified to structurally intact or disrupted anal sphincter muscles. Within each of these two groups they were then randomised to one of four groups: (1) standard medical/nursing care (advice) (2) advice plus verbal instruction on sphincter exercises (3) hospital based computer-assisted sphincter pressure biofeedback (4) hospital biofeedback plus use of a home EMG biofeedback device. Outcome measures immediately and at one year included diary, symptom questionnaire, continence score, patient’s rating of change, quality of life (SF36 and disease specific), psychological status (HAD), and anal manometry.

Results: Improvement or cure occurred in groups 1 to 4 respectively: 80%, 83%, 81%, and 76% (p=NS). Overall, 75% of patients had symptomatic improvement and 5% were “cured”. Major benefit was more likely if patients had structurally intact sphincters. Benefit was maintained for all groups at one year. Episodes of incontinence decreased from median 2 to 0 per week (p=0.001). Continence score (worst = 20) decreased from median 11 to 8 (p<0.001). Disease specific quality of life, SF36 (vitality, social functioning and mental health), and HAD (anxiety and depression) all significantly improved. Patients demonstrated improved resting, squeeze and sustained squeeze pressures (all A1 against reduction ratio) for a high AI (day 0), suggests that in the radioresistant subgroup would have a high AI. The difference between two slopes means that in radioresistant 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; radio sensitive tumours should be surgically resected earlier than the more resistant ones.

222 FAECAL CALPROTECTIN: NORMAL LEVELS IN A LATE MIDDLE-AGED POPULATION, EFFECTS OF LIFESTYLE FACTORS AND RELATION TO BOWEL SYMPTOMS

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Background: Faecal calprotectin is more sensitive but less specific than faecal occult blood (FOB) in the detection of colon 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

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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 NSAI use, units of alcohol consumed in the previous week, being a current 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.

2223 IS CONSTIPATION A CONSEQUENCE OF GROWING OLDER?

Background: The number of GP visits for constipation increases markedly among people over 60. Nevertheless, there is no good evidence that ageing per se affects colonic function. The association between age and constipation may be confounded by factors such as institutionalisation, inactivity and chronic disease.

Aim: To assess the prevalence of functional constipation according to the Rome II diagnostic criteria and institutionalisation, physical activity and chronic disease.

Methods: Ethical approval was obtained from South Bank University Ethics Committee. 50 FL subjects (mean age 74 years, range (65–97), 42% male) and 42 INS subjects (mean age 84 years, range (69–101) 36% male) were recruited. bowel habit was recorded using a 7-day bowel habit diary. Subjects were classified as constipated according to Rome II diagnostic criteria, if they experienced at least 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 t-test and Chi-square, as appropriate.

Results: Since the INS group was significantly older than the FL group, the mean ages of constipated and non-constipated subjects were assessed in each group separately. There were no significant differences in age between constipated and non-constipated subjects. Constipation was associated with institutionalisation (χ2=9.9, p=0.003) and inactivity (χ2=12.2, p=0.001). Although 65% of constipated subjects suffered from more than one chronic disease, this association was not statistically significant.

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

2244 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 its mutation causes uncontrolled cell proliferation. The aim of our study was to assess the relationship between K-ras mutations and various characteristics of colorectal polyps such as: site, size and histology.

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 (mdv1) 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 circular, tubulovillous/villous had a mutation, compared to much lower levels of mutations in tubular (9%) and metaphasic polyps (0). No difference in mutation rate was found in varying grades of dysplasia in our study.

Conclusion: 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.

2255 DO CYTOKINE LEVELS PREDICT PROGNOSIS IN COLORECTAL CANCER?
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Suppression of the immune system and cytokine production, as an essential function of the immune response, in patients with colorectal cancer has been extensively investigated. The aim of this study was to determine the predictive prognostic value of cytokine levels before and after treatment in patients with colorectal cancer.

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 coefft =0.812 at P=0.05) Similarly, those with high postoperative IFN γ levels developed local recurrence later than those with lower levels. (Correlation coefft =1at P=0.01) IL 10 & TNF α levels did not show a similar correlation. Higher levels of postoperative IL 10 levels were associated with development of metastatic disease. (Correlation coefft=0.853 at P=0.002) Higher TNF α levels before preoperative radiotherapy were associated with a longer survival in patients with rectal cancer. (Correlation coefft=0.829 at P=0.04) Similarly 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.

2266 SUCCESS OF A SIMPLE “TICK BOX” GP REFERRAL 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 referred. With 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
department. The responses allowed stratification of patients without prior assessment in outpatients into 3 groups. Patients stratified as "urgent" were sent a colonoscopy appointment for <2 weeks, "soon" for <12 weeks and routine for <36 weeks. Performance of the form has been audited over the 12 months following introduction. This included monitoring for time to colonoscopy from referral and accuracy of the form in predicting serious pathology (colorectal carcinoma, IBD).

Results: In total 691 referrals were made, of which 156 were stratified "urgent", 447 "soon" and 88 "routine". 73% of urgent patients achieved a colonoscopy in <2 weeks and 94% within 3 weeks including at peak holiday times e.g. Christmas etc. Those not done in <3 weeks were sent appointments but failed to attend. 97% of soon patients were colonoscoped in <12 weeks and 100% of "routine" in <36 weeks. See table.

Conclusions: This referral form has proved successful in identifying patients at high risk of significant pathology and has allowed appropriate targeting of resources for rapid diagnosis of pathology without prior outpatient assessment. Rates of detection of serious pathology in "soon" and "routine" referrals were not significantly higher than those that would be anticipated in a comparable unselected population.

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 noted.

Results: 149 patients are included in the study. Their average age (range) is 67(19–92). 79 were referred by 'two week criteria' and the others were reprioritised by the consultant reading the referral. Gastroscopy was performed in all cases. This was achieved in an average of 9 days (range 1–14) for those referred by 2-week criteria and 15 (range 7–35) days in those thought to meet the criteria but not referred by that route. There were 25 extra cases per month when the system was established. 14 malignancies were identified (9.4%). 12 cases were identified correctly by GP application of 2-week criteria (15.2%). 2/70 further malignancies were identified by consultant interpretation of routine referrals (2.9%).

Conclusion: The application of the 2-week criteria for upper GI cancers has led to an additional 25 procedures/month. Primary care physicians achieved a cancer pickup rate of 13.2%. Additional case finding by assessment of other referrals seems to have little additional benefit.

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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. The 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 concommitantly (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.

229 RABEPRAZOLE 20 MG COMPARED WITH ESOMEPRAZOLE 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 esomprazole (ESO) 40 mg on intragastric pH in healthy H. pylori-negative volunteers.

Methods: 27 H. pylori-negative subjects underwent two 24-hour test periods, separated by at least 14 days without, in a 2 factorial design 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 (AUC0–24) were calculated, and compared using ANOVA.

Results: There were no statistically significant differences in mean AUC0–24, 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=25.3 and 22.1%, SD=18.0; 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 C14 UREA BREATH TEST SERVICE (C14UBT)
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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. C14 based tests cannot easily be used in the community.

Aims: To assess the practicality, accessibility, appropriate use and effectiveness of a C14UBT service in the community of North Cumbria.
**Methods:** Two practices were recruited to act as local CUBT sites and clinics led by a single nurse specialist for 6 months. Criteria for referral: age >16, <45, new onset uncomplicated dyspepsia, no NSAID, no PPI. After a 4 hour fast, CO2 samples were taken at baseline and 30 minutes post ingestion of CUBT and H2RB as labelled in orange juice. CO2 samples were analysed (Cumberland Infirmary, Carlisle, PDZ Europa CUBT analyser) and result returned to GP within 24 hours. Subsequent management and outcome was monitored and nurse recorded any problems encountered during the process from referral to treatment.

**Results:** 55 referrals (34F, 21M), 17 HP+ve, 38 –ve. 78.2% were tested within 1 week of referral (10 deferred at patient request) 6 tests deferred because not fasted, 3 taken medication. 2 patients were >45, 36 patients had had symptoms for >6 months, 2 previous eradication attempts. Control ECs travelled 12 miles to his GPs surgery for a CUBT when he was working adjacent to a clinic site. All HP positive patients received eradication therapy. Post CUBT, 9.1% (3 HP+ve and 2–ve) were referred for gastroscopy, 16 (29%, 3HP +ve) received H2RB, 13 (24%, 5 HP +ve) a PPI.

**Conclusions:** Rapid HP testing was achieved with a low endoscopy rate. Changes to information sheets avoided further problems with pre test preparation. Central booking would allow patient choice of test site. These figures translate to ~1850 CUBT but only 166 endoscopies per year for this age group if extended to the whole of North Cumbria.

### Abstract 232

**ALOE VERA GEL STIMULATES PGE2 PRODUCTION AND COX2 EXPRESSION IN GASTRIC CARCINOMA CELL LINES**

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**Background:** Aloe vera gel (AV) is the mucilaginous aqueous extract from the leaf of Aloe barbadensis miller. It is a widely used herbal remedy for inflammatory conditions and digestive disorders. It is claimed to have anti-ulcer effects. Gastric epithelial cells produce COX2 and prostaglandins in response to ulceration as part of mucosal healing.

**Aims:** To determine the effects of AV on production of PGE2 and expression of COX2 by gastric epithelial cells in culture.

**Methods:** MKN7 and MKN 45 gastric cell lines were cultured in vitro in RPMI medium containing increasing concentrations of AV gel for 24 hrs. PGE2 production was measured in the culture supernatant by EUSA. Western blotting was used to detect COX2 expression by cells. Results were corrected for cell numbers estimated by MTT assay.

**Results:** Incubation of both MKN7 and MKN 45 cell cultures with AV 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.

**Conclusions:** 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

**PEPTIC ULCER IN GENERAL PRACTICE IN ENGLAND AND WALES 1994–1998: A DISEASE IN DECLINE**

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**Background:** While hospital admission rates in England and Wales for complicated peptic ulcer has increased among older people, little is known about its prevalence in the community.

**Aims:** To analyse recent time trends in England and Wales in the prevalence of peptic ulcer, based on the proportion of the population who had been seen either by the general practitioner or a hospital doctor, during each one-year period. The drug treatment for peptic ulcer was also studied.

**Methods:** For each year between 1994–98, information on the age, sex and drug treatment for patients with peptic ulcer was extracted from the General Practice Research Database. Age-sex specific prevalence and treatment rates were then calculated.

**Results:** See table. The decline in age-standardised prevalence was more evident among people aged less than 65 (60% for males,
A PROSPECTIVE STUDY OF GASTROENTEROLOGY CONSULTATIONS IN AN URBAN TEACHING HOSPITAL

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Consultation between individual specialties 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-patient consultations 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 for subsequent problems was less than one working day. Referral reasons for PEG tube insertion 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. Most clinical problems assessed were dealt with satisfactorily in a consultation setting, with only a minority requiring transfer to a Gastroenterology team during inpatient stay but a significant percentage required endoscopic procedures and follow up at a GI clinic after discharge. Consultations for PEG tube insertion were especially worthwhile.

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

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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 injury.

Patients and Methods: 18 patients (13 females, median age 23 years; range 14-42) with major burn injury (Burn surface area >20%) admitted over 20 months were analysed. The aetiology was flame burns (10), hot water burns (5) and acid burns (3). All patients were received within 6 hours of injury. Initial fluid resuscitation was performed according to Parkland regime. Non-steroidal anti-inflammatory drugs and acid suppression were not employed. All patients were subjected to upper gastrointestinal endoscopy (UGIE) between 24-72 hours after admission and antral mucosal biopsy was obtained. UGIE was repeated a week later. Histology samples were evaluated by a single blinded pathologist. Dyspeptic symptoms were sought on a daily basis.

Results: 2(11.1%) Patients had mild upper abdominal pain.
2(11.1%) Patients had abnormal UGIE findings during the first endoscopy. 1 [perforated gastric ulcer]; 1 [erosive gastritis]. 3(16.7%) Patients had abnormal endoscopic findings during subsequent endoscopy: 2 [perforated gastric ulcer, erosive gastritis]. No peptic ulcers were detected in any of the patients. 8(44.4%) Patients had mild histological changes [mild acidic inflammatory changes, chronic inflammatory changes].

Conclusion: This study shows that there was no endoscopic evidence of serious gastroduodenal mucosal injury in patients with major burns. Furthermore, antral mucosal histology revealed only mild inflammatory changes. The use of prophylactic acid suppression in major burns as a blanket policy may require re-evaluation.

NSAID AND PEPTIC ULCER DISEASE: A RANDOMIZED TRIAL OF OMEPRAZOLE 20 MG VERSUS 10 MG FOR MAINTENANCE OF REMISSION AFTER PEPTIC ULCER HEALING AND HELICOBACTER PYLORI ERADICATION

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Background: The role of H. pylori eradication in NSAID users with peptic ulcer disease is controversial especially in countries with a high prevalence of the infection. Also the role of low dose Omeprazole for maintenance of remission is not yet known.

Patients and methods: 138 symptomatic outpatients receiving continuous Cox 1 NSAID therapy, were treated with Omeprazole 40 mg/day upon endoscopic confirmation of gastro-duodenal ulcer or erosions while those infected with H. pylori received in addition Clarithromycin 500 mg and Amoxyclillin 1000 mg twice daily during the first week of treatment. After endoscopic confirmation of healing at the end of week 5 (n=116), the patients were randomised to receive Omeprazole 20 mg once daily (n=50) or placebo (n=64) and endoscopy repeated after 20 weeks. No patients discontinued treatment because of adverse effects of the drugs and efficacy results are for patients completing the trial protocol.

Results: The overall healing rates at five weeks (n=130) was 89.1% (95% confidence limits 84.7-93.5) while in 86.3% (81.2-89.1) healing 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=54) it was 96.1% (NS). After 20 weeks of Omeprazole prophylaxis with the 10 mg 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).

Conclusion: In a Middle Eastern population with NSAID induced gastro-duodenal ulcer disease, H pylori eradication and high dose Omeprazole treatment were not associated with impaired ulcer healing. After eradication, Omeprazole 20 or 10 mg per day were highly and equally effective for maintenance of gastro-duodenal mucosal integrity during continued NSAID use.

WARFARIN ANTI-COAGULATION CONTROL IN PATIENTS TAKING PROTON PUMP INHIBITORS

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Background: There is evidence that proton pump inhibitor (PPI) use can increase the prothrombin time in healthy volunteers taking warfarin. However, no studies have been carried out to investigate the effect of PPIs on anti-coagulation (AC) control in patients requiring warfarin therapy. Therefore we tested the hypothesis that PPI therapy worsens AC control in patients attending an AC Clinic.

Methods: The Leeds AC Clinic database was analysed retrospectively. We collected data on patient age, indication for and duration of AC, PPI use and warfarin dose. We also obtained all the INR values for each patient. INR control was expressed as the percentage of INR values above, within or below the target range for each individual.

Results: 14.8% (n=503) of patients were taking a PPI (omeprazole, n=310 [61.7%]; lansoprazole, n=167 [33.2%]; pantoprazole, n=13 [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<0.01; Student’s t test) 52.6% (p<0.001) and 29.8% (p=0.32). However there was no significant difference in mean INR value, warfarin dose or duration of therapy between the two groups. The two groups did differ with respect to age (PPI, mean 72.4 yrs vs non-PPI, 70.8 yrs; p=0.005) and frequency of INR testing (PPI, every 53 days vs non-PPI, every 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 antiepileptics as well as on clinically significant bleeding episodes, is warranted.

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

S. Aroori, 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 G.I surgeons across United Kingdom inquiring the following: (1) The pathological conditions in which they chose to eradicate the organism - Gastric atrophic pangastritis and gastritis, gastrectomy, gastric surgery, duodenal ulcer, peptic ulcer disease, and H pylori infection. (2) The type of regimen used.

Results: One hundred and sixty-two (61.5%) gastroenterologists and sixty-two (47.5%) surgeons replied to the questionnaire. The overall 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 radiology and GORD. Fifty gastroenterologists (62.5%) and thirty-two (51.6%) surgeons did not recommend eradication therapy for patients with radiology while 47.5% of gastroenterologists and 53% of surgeons did recommend eradication in patients with radiology. 24% of gastroenterologists and 18% of surgeons had not considered eradication at all in gastritis while in patients with gastroduodenitis, 17.5% of gastroenterologists and 11.3% of surgeons did not favour eradication of the organism. Majority of surgeons and gastroenterologists favoured triple therapy using combination of Proton Pump Inhibitor, Clarithromycin and Amoxicillin.

Conclusions: In this study, we have noted wide variations in the practice of gastroenterologists and surgeons across United Kingdom in advising eradication therapy for H. pylori positive patients in various upper GI conditions. While there is a general consensus in the mode of therapy offered, there seems to be varied practice in eradication of the organism in conditions such as NUD and GORD.

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

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Background: Although long-term treatment with proton-pump inhibitors is generally considered safe, there is still little evidence from prospective studies about the effect of such treatment on the gastric mucosa.

Objectives: The primary objective was to assess efficacy in preventing GORD relapse. The secondary objective reported here was to assess the effect of 5 years’ treatment with rabeprazole or omeprazole on the gastric mucosa.

Methods: 243 patients were randomised to double-blind treatment with rabeprazole (10 mg or 20 mg) or omeprazole (20 mg) once daily for 5 years. Biopsy samples were taken from the corpus and antrum after 13, 26, and 52 weeks, and annually thereafter.

Results: The percentage of patients with H pylori infection fell substantially during the study in all groups, but only in the 10 mg rabeprazole group in the corpus. Inflammation, activity of inflammation, and mast cell numbers 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 changed 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 omeprazole 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.

THE INFLUENCE OF SMOKING AND NSAIDS ON SYMPTOM SEVERITY IN PATIENTS TAKING ANTISECRETORY THERAPY

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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 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 NSAID, 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>Abstract 240</th>
<th>% patients</th>
<th>Mean GDSS</th>
<th>Mean DDQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>15.2</td>
<td>5.36*</td>
<td>2.57</td>
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<tr>
<td>No NSAIDs</td>
<td>69.8</td>
<td>5.87</td>
<td>2.62</td>
</tr>
<tr>
<td>Other NSAID</td>
<td>12.2</td>
<td>5.88</td>
<td>2.57</td>
</tr>
<tr>
<td>Aspirin-Other NSAID</td>
<td>3.0</td>
<td>5.94</td>
<td>2.41*</td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>39.3</td>
<td>5.83</td>
<td>2.60</td>
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<tr>
<td>Ex smoker</td>
<td>25.2</td>
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<td>2.61</td>
</tr>
<tr>
<td>Current smoker</td>
<td>35.6</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 NSAID, 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.

NSAID PRESCRIBING GUIDELINES: CONTINUED ULCER BLEEDING DESPITE MANAGEMENT CONSENSUS

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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-varical upper gastrointestinal haemorrhage (53 men; mean age
60+×2.1, range 18–96). Ten patients were on non-aspirin NSAIDs (four men, mean age 52±8, 18–96) of whom three were on lower-risk formulations. None of these ten patients were co-prescribed gastro-protective drugs, one patient each was on aspirin and corticosteroids in addition to the NSAID. Eight patients on NSAID had significant co-morbid disease, five of whom were aged over 65 years. No patient on NSAID had a history of PUD. Twenty-three patients (17 aged ≥ 65, 2 with PU history) were taking aspirin. Only one was co-prescribed a gastro-protective drug.

Summary: Patients who presented with an upper GI bleed while on NSAIDs were not prescribed NSAIDs in accordance with locally agreed guidelines. NSAID-associated ulcer complications could be reduced by better prescribing.

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242 IDENTIFICATION OF POSSIBLE GUT HOMING DENDRITIC CELLS IN PERIPHERAL BLOOD BY EXPRESSION OF β7 INTEGRIN

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Dendritic cells (DC) are amongst the earliest cells to recognise enteric antigens and shape T cell responses. At least in part, DC in the tissues are derived from immature circulating DC populations. Gut DC may be functionally different from DC at other sites and contribute to the special features of intestinal immune responses. Given that there are markers on peripheral blood DC precursors that identify skin homing DC (CD1c and CLA), this study aimed to identify peripheral blood DC destined to home to the gut. We examined DC expression of β7, an integrin associated with mucosal homing of lymphocyte populations.

Methods: DC were identified by multi-colour flow cytometry as an HLA-DR-lineage [CD3, CD14, CD16, CD19, CD34, CD56] population in peripheral blood and in mononuclear cells extracted from the lamina propria of the colon or small intestine. Co-expression of β7 with CD11c, CD1c and CLA was assessed.

Results: Gut DC from both the small and large intestine expressed β7 integrin. In blood, most DC expressed β7 but they were heterogeneous for the level of expression and for co-expression of the molecules associated with skin homing. Both myeloid and plasmacytoid DC were studied. All CD11c+ ‘myeloid’ DC were β7+, with some also expressing skin homing molecules. CD11c+ ‘plasmacytoid’ DC, which are thought to migrate directly into lymphoid tissue, comprised two subpopulations, β7hi and β7lo. Neither of these populations expressed the skin homing markers CLA or CD1c.

Conclusions: It appears that DC with markers associated with homing to the gut mucosa can be identified in the peripheral blood. A population of DC, β7hi CD11c+, that may migrate directly into lymph nodes draining the gut, has been identified. Circulating precursors of gut DC that are functionally committed to specialised roles in the intestine may provide an early target for manipulating mucosal immune responses.

243 NEUTROPHIL RESPIRATORY BURST AND TISSUE PENETRATION ARE NORMAL IN CD DURING G-CSF ADMINISTRATION

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Background: Neutrophil migration into the tissues is defective in Crohn’s disease (CD). Granulocyte Colony Stimulating Factor (G-CSF) has been used to treat CD. The effects of G-CSF in CD on venous neutrophil respiratory burst (B) and neutrophil tissue penetration (P) are unknown.

Aim: To measure B&P in CD and matched control subjects.

Method: 16 outpatients were enrolled [CD n=8, 4518 years, 3 male; control: n=8, 4217 years, 7 male]. Subcutaneous G-CSF (Lenograstim) 5µg/kg was administered at 24 & 48 hours. Venous neutrophils were purified at 24 & 72 hours by Hypaque-Ficoll gradient centrifugation after erythrocyte osmotic lysis. Oxygen consumption of neutrophils were purified at 24 & 72 hours by Hypaque-Ficoll gradient centrifugation after erythrocyte osmotic lysis. Oxygen consumption of venous neutrophil number (CD11b+) was assessed.

Results: Increase in venous monocyte concentration was reduced in CD subjects at 72 hours [1.2±1.1 x 10³/µl; CD 0.1±0.1 (p=0.03)], B&P were normal in CD. However in all subjects, B was significantly reduced after G-CSF (flora challenge from 87±8 to 44±6.9 [n.mol.O₂/10⁶ neutrophils/min] (p=0.008); PMA challenge from 64±8 to 26±3.4 (p=0.002)). P was markedly lower than initial venous neutrophil concentration (CD 21±1%) and controls (14±5%). P increased with G-CSF (CD from 0.7±0.6 to 3.4±2.5, 10³CD16/µl) (p=0.02); controls from 0.5±0.4 to 3.7±0.6 (p=0.02) but proportionally less than the increase in venous neutrophil number (CD 12±5%) and controls (15±6%).

Conclusion: Efficacy of G-CSF in CD will be affected by the reduction in B. The increase in P during G-CSF does not parallel the increase in venous neutrophil number.

244 STREPTOCOCCUS FAECIUM, A POSSIBLE PROBIOTIC BACTERIUM, BUT NOT LACTOBACILLUS ACIDOPHILUS OR ESCHERICHIA COLI (NISSELE), DECREASES PROINFLAMMATORY CYTOKINE PRODUCTION (IFN-γ) BY AN IL-10 DEPENDENT MECHANISM

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Introduction: Probiotics are effective in the treatment of some inflammatory bowel diseases, but their mechanism of action is unclear.

Methods: A whole blood assay was developed to assess the effect of probiotic bacteria on gamma-interferon (IFNy) production by polyclonally activated T-cells. Cell wall and soluble fractions of Lactobacillus acidophilus, Streptococcus faecium and Escherichia coli (Nissele strain) at the equivalent of 10⁹ 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 IFNy 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 IFNy producing CD8+ and CD8-T cells. IFNy production was not altered by the other probiotics. Cell activation assessed by CD69 expression was not affected. The inhibition of IFNy 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 T-cell IFNy 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 populations.

245 ASCA AND ANCA IN THE DIAGNOSIS OF INFLAMMATORY BOWEL DISEASE AND OTHER DIARRHOEAL ILLNESSES

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Background: Several studies have examined the utility of ASCA and ANCA either alone or in combination for aiding the diagnosis of inflammatory bowel disease (IBD). ASCA and ANCA in combination are said to be more specific than either alone. ANCA-ASCAs+ is the
result expected in Crohn’s and ANCA+ASCA+ in UC. We have tested the utility of ASCA or ANCA alone or in combination in distinguishing between IBD and other diarrhoeal illnesses.

Methods: 150 sera from patients attending a gastroenterology clinic with diarrhoeal disease were screened for ASCA using the GENESIS IgA and IgG ASCA kits, and for ANCA by indirect immunofluorescence on ethanol fixed neutrophils. Patients were classified as Crohns, UC or other diarrhoeal independence, independently of the ANCA/ASCA results, according to standard criteria.

Results: IgA ASCA alone has a sensitivity of 0.44 and specificity of 0.94 for Crohn’s disease [0.44/0.94]. Increases in sensitivity are accompanied by reduction in specificity when IgG ASCA [0.58/0.85] or IgG ASCA/ANCA [0.52/0.90] in combination are added. ANCA alone has a sensitivity of 0.54 and specificity of 0.85 for the diagnosis of UC. The addition of ASCA does not affect sensitivity or specificity (0.54/0.86).

Conclusions: (1) The high sensitivity of IgA ASCA for Crohn’s suggests that the presence of this antibody should trigger appropriate further investigation. However, its low specificity means that a negative result does not exclude Crohn’s. For this reason, the low specificity resulting from adding IgG ASCA or ANCA will result in a loss of utility, despite the increase in sensitivity. (2) The low sensitivity and specificity of these assays for UC suggests that their utility in this setting is low. (3) While IgA ASCA screening may have value in diagnosing Crohn’s, IgG ASCA and ANCA are not useful in routine diagnosis of patients with diarrhoeal disease.

246 INCREASED EXPRESSION OF α-DEFENSINS WITH INCREASING SEVERITY OF TROPICAL ENTEROPATHY

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Background: Tropical enteropathy is a term used to describe a different villous and crypt architecture to that seen in temperate climates. Its occurrence is low. (3) While IgA ASCA screening may have value in diagnosing Crohn’s, IgG ASCA and ANCA are not useful in routine diagnosis of patients with diarrhoeal disease.

Methods: Biopsies (n=84 in the first year, n=44 second year and n= 36 third year) were obtained from a longitudinal study of enteropathy and infection in an impoverished township in Misisi, Zambia. Defensin mRNA was quantified by competitive RT-PCR (expressed as log transcripts /µg total RNA). mRNA and peptide expression was localised by (expressed as log transcripts /µg total RNA). mRNA and peptide expression was localised by immunoblotting and immunostaining. Immunoblotting was used to analyse expression of HDS and HD6 isoforms.

Results: Peptide and mRNA expression were only seen in the enteropathy group. A significant proportion of patients on acid suppression therapy, and 106 patients with gastro-oesophageal cancer were genotyped by PCR and restriction enzyme digest to determine their capacity to metabolise PPIs. The benign group was further subdivided according to H. pylori status and presence of peptic ulcer.

Conclusions: Increased severity of tropical enteropathy correlated with increased quantity of α-defensin mRNA in jejunal biopsies, consistent with the hypothesis that tropical enteropathy is an adaptive response to microbial challenge.

247 THE CLINICAL SPECTRUM OF GASTROINTESTINAL INVOLVEMENT IN PATIENTS WITH PRIMARY HUMORAL IMMUNODEFICIENCY; A CLINICAL SURVEY OF PATIENTS FROM IRANIAN PRIMARY IMMUNODEFICIENCY REGISTRY

Aghaamhamedali Asghar, Moein Mostafa, Farhoudi Abolhasan, Pourpak Zahr, Rezaei Nima, Abolmaali Kamran, Movahedi Masoud, Gharagozlou Mohammad, Mahmodi Maryam, Hojati Ashraf Tah. Department of Immunology, Allergy and Asthma, Children Medical Center Hospital, Tehran University of Medical Sciences

Background: Primary Humoral ImmunoDeficiencies (PHID) are currently increasingly recognized, thanks to novel advances in the immunology and its laboratory techniques. Gastrointestinal involvement, together with respiratory infections, account for most of the complications and the main cause of hospitalizations in such patients.

Objectives: To determine the clinical spectrum of gastrointestinal involvement in patients with PHID.

Method: We have reviewed the data from the clinical files of patients with PHID, diagnosed according to WHO criteria, who were enrolled in Iranian Primary Immunodeficiency Registry.

Results: We analyzed 125 patients (84 males), with the diagnoses of primary antibody deficiency including common-variable immunodeficiency (64 pts), x-linked agammaglobulinemia (29 pts), IgA deficiency (20 pts), IgG subclass deficiency (8 pts), and hyper-IgM syndrome (4 pts). The mean age of the patients at the time of study was 11 years. In the evolution of their disease, 78 cases (62.4%) have had involvement. Diarrhea, being the most common type of involvement was seen in 70 patients (56%). Seventeen of these patients (24.2%) have progressed to chronic diarrhea. Giardiasis and hepatitis were seen in 12 (9.6%) and 7 (5.6%), respectively. Also, we had 5 cases of chronic active hepatitis and 3 cases of ulcerative colitis. Among nonspecific symptoms, hepatomegaly was seen in 32 patients and splenomegaly in 28 patients. Celiac disease was seen in 2 cases with the diagnosis of selective IgA deficiency.

Conclusion: Following the respiratory tract, gastrointestinal tract constitute the second site of involvement in patients with primary humoral immunodeficiency. Even some patients may present with recurrent diarrhea as the first manifestation of immunodeficiency disorders.

248 THE RESPONSE TO PROTON PUMP INHIBITOR THERAPY IS GENETICALLY DETERMINED

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Objective: The metabolism of PPIs by the CYP2C19 enzyme is genetically determined with considerable inter-individual variation. The aim of this study was to establish the relative frequencies of fast, medium and slow metabolisers, and to examine PPI dose with respect to metabolic capacity.

Methods: 535 patients with benign acid disorders on acid suppression therapy, and 106 patients with gastro-oesophageal cancer were genotyped by PCR and restriction enzyme digest to determine their capacity to metabolise PPIs. The benign group was further subdivided according to H. pylori status and presence of peptic ulcer.

Results: The frequency of each metabolic group was similar in the benign and cancer patients. Rapid Extensive (fast) metabolisers 75.3% of benign, 76.4% of cancer; Extensive (medium) metabolisers 23.7% benign, 20.8% cancer; Poor (slow) metabolisers 2.8% benign, 2.8% cancer. Thus 26.5% of patients on acid suppression therapy are medium or slow metabolisers and have a reduced capacity to metabolise PPIs. In the H. pylori negative peptic ulcer group 87.5% of the fast metabolisers were on 20mg omeprazole and 12.5% were on 10mg. This may be a reflection of lack of symptomatic response to a lower dose. In the medium / slow group 53.8% were on 20mg omeprazole, and 46.2% on 10mg (p=0.023, x2 test).

Conclusions: A significant proportion of patients on acid suppression therapy have a reduced ability to metabolise PPIs. These patients may require a lower dose of PPI. The clinical implications are treatment failure for fast metabolisers on low dose PPI, and adverse effects and unnecessary financial cost in the medium / slow metabolisers.

Abbreviations: PPI = proton pump inhibitor, PCR = polymerase chain reaction.
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 an 14C urea breath test. 3,244 individuals (2,165 HP–ves, 1,079 HP+ves) supplied medication details on a validated questionnaire. Inhaled/oral bronchodilators, inhaled corticosteroids or omeprazole 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 (adjusted OR 0.75 (0.57–0.99), p<0.05).

Conclusions: Childhood infection with Helicobacter pylori is associated with a reduced risk of atopic disorders in adult life.

250 PROBIOTIC BACTERIA STIMULATE NATURAL KILLER (NK) CELL ACTIVATION AND CYTOKINE PRODUCTION, AN EARLY STEP IN INNERVATE IMMUNITY

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Introduction: Probiotics are effective in the treatment of inflammatory bowel diseases, but their mechanism of action is unclear. Given that NK cells have a central regulatory role in host defence against bacteria, in particular models of colitis, we studied the effect of probiotic bacteria on NK cell activation and cytokine production.

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

Results: At high concentrations (105 colony forming units per millilitre), cell wall fractions of all three probiotic bacteria induced expression of CD69 on 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. IFNγ, 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 a baseline expression of CD69 of >90% 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 mediate 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.

251 INTERFERON-γ BLOCKS THE INTERLEUKIN-1 AND BACTERIALLY MEDIATED INDUCTION OF HUMAN β-DEFENSIN 2 EXPRESSION IN GASTRIC AND INTESTINAL EPITHELIAL CELLS

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Introduction: β-defensins are endogenous antibiotics secreted by the epithelia of mucosal surfaces, where their expression is augmented by infection and inflammation. We have previously shown marked induction of human β-defensin 2 (BD2)-2 expression in gastric and intestinal epithelial cell lines by various pathogenic stimuli. In the present study we have explored the role of IFN-γ; one of the major cytokines expressed during chronic Th1-mediated GI inflammation (e.g. Crohn’s disease), in the regulation of BD2 gene expression.

Methods: BD2 mRNA expression was quantified by RT-PCR. Immunohistochemistry was performed on archival paraffin-blocked samples from patients with varying grades of gastritis (grade II/III) and from IBD [inflammatory bowel disease] tissue.

Results: In marked contrast to the known stimulatory effect of IL-1 on hBD2 expression, IFNγ did not induce hBD2 in a panel of gastric and intestinal cell lines. Interestingly, pre-exposure of cells to IFNγ completely abolished the effects of IL-1 and pathogenic-stimuli on hBD2 gene expression. This inhibitory effect of IFNγ was however, time-dependent. We also observed an inverse relationship between defensive peptide expression and the degree of inflammation in biopsy samples.

Conclusions: Our present study suggests that during Th1-driven chronic GI inflammation, IFNγ may act as a biological ‘off-switch’ for hBD2 expression. Downregulation of host innate defence during infection and inflammation may represent one strategy employed by potential pathogens in evading the host immune response.

252 DYSPESIA IS MORE COMMON IN ELDERLY WOMEN

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

Aims: To conduct a questionnaire survey of the general population over 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 simple sheet questionnaire. This ascertained basic demographic details and asked whether subjects suffered from heartburn, nausea, upper abdominal pain or heartburn on more than one occasion or for more than a day in the previous month. Participants were also asked how often they took any medication for these symptoms and requested to send a sample of saliva collected in a cotton salivette (Sarstedt) by post of return. The saliva samples were analysed for antibodies to HP in order to determine seropositivity as previously described (Gut 2000; 46 [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 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 (heartburn). HP infection was detected in 25% of both these groups. The prevalence of dyspeptic symptoms was not related to HP seropositivity, age, smoking, social class, BMI nor NSAID use. It was more common in women (51 vs 39%, p<0.0001). In particular women had more symptoms of bloating (25 vs 13%, p< 0.0001) and nausea (11 vs 5%, p< 0.015). These differences remained significant even after subjects on occasional or regular medication for dyspepsia were excluded from the analysis.

Conclusion: The prevalence of self reported dyspepsia in older individuals is high, and is more common in women. It is not related to NSAID use, smoking or HP infection, and deserves further investigation.

253 CHOLERA TOXIN (CT), ESCHERICHIA COLI HEAT LABILE (LT) AND HEAT STABLE TOXIN (STA) HAVE AN INDIRECT EFFECT ON DISTAL INTESTINAL FLUID TRANSPORT IN THE RAT SMALL INTESTINE

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Background: CT, LT and STA induce intestinal secretion directly via cyclic AMP and cyclic GMP dependent pathways respectively. Increasing evidence exists that these enterotoxins may mediate intestinal secretion through a local intramural neural reflex arc. To investigate this neural enterotoxin-induced intestinal fluid transport we measured the effects of CT, LT and STA on intestinal fluid and electrolyte transport in distal non-contiguous and transected intestinal segments separately.

Methods: A model of distal aboral secretion was created in anaesthetised 200g male Whistar rats. CT (50 µg/ml), LT (50 µg/ml), STA (2µg/ml) and saline [control] were placed independently in a proximal intestinal loop (an isolated 15cm jejunal loop) separated from a distal intestinal loop (a 5cm ileal loop) by tissue glue (Infernal); the lumina were then isolated to measure changes in fluid and electrolyte transport. The experiment was repeated with the distal loop transected, for each enterotoxin.
**Abstract 255**

<table>
<thead>
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<td>*830</td>
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<td>(±81)</td>
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<td>IL-8 (pg/ml)</td>
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<td>(±21)</td>
<td>(±18)</td>
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</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 nerves. Transection of the intestinal wall abolished the distal effect on intestinal transport by CT, LT and STa supporting the hypothesis that intrinsic intramural neurons play a key role in enterotoxin-induced intestinal secretion. Further work is required to define the circuitry of these intrinsic neural pathways.

**Abstract 254**

**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**

R. Rigby1, M.A. Kamm2, S.C. Knight1, A.L. Hart1, A.J. Stagg3. 1APRG, Imperial College; 2St Mark’s Hospital, London, 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 bacterial products, and results in a balance between pro- and anti-inflammatory responses. IL-12 is produced by pathogenic bacteria, whereas IL-10 is produced by probiotic 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 mononuclear cell preparations obtained by collagenase digestion of colonic tissue. Production of IL-12, IL-10 and IL-4 in response to LPS stimulated cultures, downregulated production of IL-12, and stimulated a primary mixed leucocyte reaction. IL-4 production by DC was not affected by the addition of LPS (1µg/ml). After overnight incubation (37°C, 5% CO2), cells were re-suspended in RPMI to a final concentration of 1x10^6 cells/ml. The cells were then pre-incubated with the NO donor L-arginine (G-SNAP-1) over a concentration range of 0 to 1mM for 30 mins prior to stimulation with LPS (1µg/ml). The cells were then stimulated with LPS (1µg/ml) and 1 ng/ml recombinant TGF-β1. After overnight incubation (37°C, 5% CO2), the cells were centrifuged and the supernatant IL-12 and TNF-α concentrations measured using specific bioassay and ELISA respectively.

**Results:** See table for TGF-β and IL-8 conc. in culture supernatants, as determined by intracellular staining. CD11c+MHC class II+ 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 stimulated cultures, downregulated production of IL-12, and stimulated a primary mixed leucocyte reaction. IL-4 production by DC was not affected by the addition of LPS (1µg/ml). After overnight incubation (37°C, 5% CO2), cells were re-suspended in RPMI to a final concentration of 1x10^6 cells/ml. The cells were then pre-incubated with the NO donor L-arginine (G-SNAP-1) over a concentration range of 0 to 1mM for 30 mins prior to stimulation with LPS (1µg/ml). The cells were then stimulated with LPS (1µg/ml) and 1 ng/ml recombinant TGF-β1. After overnight incubation (37°C, 5% CO2), the cells were centrifuged and the supernatant IL-12 and TNF-α concentrations measured using specific bioassay and ELISA respectively.

**Conclusions:** In intestinal epithelial cells, (i) exposure to low concentrations of toxin A induces the release of TGF-β1, which facilitates recovery of barrier function (ii) exposure to high concentrations of toxin A induces the expression of the neutrophil chemoattractant IL-8 and rapid, irreversible loss of barrier function. Thus the level of exposure of intestinal epithelial cells to C. difficile toxins may determine the development and severity of colitis.

**Abstract 256**

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

J. Burdass1, J. Smith, C.J. Hawkey. University of Nottingham, Division of Gastroenterology, UK

**Introduction:** NO donating anti-inflammatory drugs such as NON-NSAIDS and Nitropripresnilone 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-1ß 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 1x10^6 per ml. The cells were then pre-incubated with the NO donor G-SNAP-1 over a concentration range of 0 to 1mM for 30 mins prior to the addition of LPS (1µg/ml). After overnight incubation (37°C, 5% CO2), the cells were centrifuged and the supernatant IL-1ß and TNFα concentrations measured by ELISA (R&D DuoSet).

**Results:** There was a dramatic and highly significant inhibition of IL-1ß but not TNFα release in a concentration related response (p<0.001 One Way ANOVA analysis, IL-1ß IC50 = 61.7µM, SEM 0.04) (see fig).

**Conclusion:** NO released from G-SNAP-1 is a potent inhibitor of pro-inflammatory mediator IL-1ß production by human PBMC’s but not TNFα.
DIAGNOSTIC YIELD OF STOOL ANALYSIS AND ENDOSCOPY IN HIV POPULATION PRESENTING WITH DIARRHOEA

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Background: HIV patients commonly attend with history of diarrhoea. The use of highly active antiretroviral therapy (HAART) has led to a change in the epidemiology of diarrhoea in HIV patients. The patients with negative stool studies are frequently referred for endoscopic evaluation. We aimed to determine the diagnostic yield of stool analysis and endoscopy in HIV patients presenting with diarrhoea.

Methods: We retrospectively reviewed 525 HIV positive patients who presented with diarrhoea from January 1, 2000 to August 31, 2001 at Chelsea & Westminster hospital. Patients were divided in 3 groups - Group 1) CD4 count ≤ 200 , 2) CD4 >200 - <350 3) CD4>= 350. Patients who had 2 or more stool examinations were included. We also reviewed the endoscopy and biopsy findings of the patients who had negative stool studies.

Results: Of 86 patients with CD4 count ≤ 200 (Group 1) the stool examination was diagnostic in 30 patients (34.8%) - the commonest diagnosis being cryptosporidiosis (10 patients -11.6%), other causes were E histolytica, giardiasis, campylobacter, salmonella, C difficile, toxoplasma, isospora, rotavirus. Of 30 patients, 12 patients (40%) were on HAART, however only 2 patients (20%) presenting with cryptosporidiosis were on HAART. In group 2 (CD4 >200 - <350 ) and group 3 (CD4>= 350), diagnostic yield of stool examination was in 37 patients(24.34%) and 74 patients (25.78%) respectively. The cause most frequently found in group 2 and group 3 was giardiasis (14 patients - 9.2%) and campylobacter (20 patients -6.9%) respectively. 64 patients (16.6%) with negative stool studies were referred for endoscopy. Upper GI endoscopy and lower GI endoscopy with biopsies was diagnostic in 12 (30%) and 19 (50%) patients respectively.

Conclusion: In our population stool analysis in HIV patients with higher CD4 count has a low diagnostic yield. With the advent of HAART the infectious causes of diarrhoea are probably less important. Our study also showed that upper and lower GI endoscopies with biopsies are useful diagnostic investigations in patients with chronic diarrhoea.

Inflammatory bowel disease posters 258-298

DOES THE INITIAL HEALTH PERCEPTION OF IBS PATIENTS,Recorded at the Time of Diagnosis, Change Over the Following Two Months, and How Valuable is this Health Perception in Predicting Outcome? A PILOT STUDY

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Introduction: Irritable Bowel Syndrome (IBS) is a common condition affecting up to 30% of the population. The determinants relating to the uptake of primary and secondary medical care are unclear although IBS patients referred to secondary care have been found to have greater severity of symptoms, greater psychiatric-comorbidity and more negative health beliefs about their illness such as death phobia and catastrophizing. It is unclear whether these health beliefs are pre-existing or develop in response to the symptoms or perhaps in response to having negative test results. This study analyses the health perception [Leventhal et al. 1980; 1984] of IBS patients at the time of diagnosis and again two months later.

Methods: Thirty-five patients with IBS were recruited from the out-patient clinic of the Gastroenterology Department of the Kent and Canterbury Hospital, Kent. Each patient was recruited on their first visit to the gastroenterologist and completed a brief demographic questionnaire. A diagnosis of IBS was determined after taking a complete history of the patient, and receiving clear test results from barium enema or colonoscopy and from bloods. Patients completed the illness perception questionnaire within the first couple of weeks of receiving their IBS diagnosis. Two months later, these patients were contacted again and asked to complete the illness perception questionnaire, the hospital anxiety and depression scale and questions relating to their perceived quality of life and satisfaction with health.

Results: The individual components of the health perception: psychological cause, external 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.

Conclusion: 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

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Introduction: Smoking is an established risk factor for the 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.

Conclusion: 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.

Abstract 259

<table>
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<th>Disease</th>
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<th>Ex-smokers</th>
<th>Non-smokers</th>
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<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>
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<td>Colonic</td>
<td>49</td>
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</tbody>
</table>

Conclusion: Patients with isolated colonic CD are less likely to be smokers at presentation than those with mixed small/large bowel disease (p=0.0001, OR=2.45, 95%CI: 1.66–3.63). Significance remains, comparing isolated colonic with ileo-caecal/SBD (p<0.0001, OR=3.71, 95%CI: 1.77–4.14).

OUTCOME OF ENTERAL FEEDING FOR NEWLY DIAGNOSED CROHN’S DISEASE

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Introduction: Induction of remission in Crohn’s disease can be achieved with exclusive enteral nutrition (EN) or oral steroids. It has been suggested that EN only delays the inevitable use of steroids.
this study we have followed up the outcome of children newly diagnosed in our unit with Crohn’s disease.

Methods: The case notes of patients newly diagnosed with Crohn’s disease during 1999 and 2000 were reviewed in August 2001.

Results: Patients: 36 patients new patients were diagnosed with a median age of 12.9 years (range 6.67–15.0). 22 had small bowel and colon affected, 7 had small bowel alone and 2 had colonic disease alone. 31/36 had disease severity requiring treatment with EN or steroids. The remaining 5 had localised oral/perianal disease not requiring EN or steroids. Initial treatment: Exclusive polymeric EN (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 steroids. 7/27 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 children. During the period of follow up 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.

LOW DOSE ORAL METHOTREXATE FOR THE MEDICAL ROLE OF THE 5Q31 CYTOKINE CLUSTER (IBD5 LOCUS) APHTHOUS ULCERATION IN THE COLON AFTER COMBINATION IMMUNOMODULATORY THERAPY

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

Background: Cyclosporin is a fungal metabolite and is a powerful immunosuppressant. While response to intravenous steroids is in excess of 60%, the remainder of patients are left with the options of curative panproctocolectomy 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 3.4 years (range 0.9–25 years). All patients were treated with cyclosporin at a dose of 4mg/kg/day. Nine patients were simultaneously started on oral aza-thioprine (median dose 1.8mg/kg). Seven patients underwent surgery (panproctocolectomy), 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.

LOW DOSE ORAL METHOTREXATE FOR THE MEDICAL ROLE OF THE 5Q31 CYTOKINE CLUSTER (IBD5 LOCUS) APHTHOUS ULCERATION IN THE COLON AFTER COMBINATION IMMUNOMODULATORY THERAPY

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

Results: Sodium picosulphate was used in 124 colonoscopies and sodium phosphate in 51. The groups were evenly matched for age and sex. Aphthous ulceration was documented in 4/124 (3.2%) after sodium picosulphate but 7/51 (13.7%) after sodium phosphate (p=0.015; Fisher’s Exact Test). The incidence of ulceration in patients known to have inflammatory bowel disease was only 3/27 and the incidence of ulcers was only significantly increased in the group whose indication for the exam was altered bowel habit. (1/24 [4.2%]; 6/23 [26.1%] (p=0.048; Chi squared test).

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

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 colonoscopies (mean dose 14.1 wks/mg) 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 known to have inflammatory bowel disease was only 3/27 and the incidence of ulcers was only significantly increased in the group whose indication for the exam was altered bowel habit. (1/24 [4.2%]; 6/23 [26.1%] (p=0.048; Chi squared test).

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

ROLE OF THE 5Q31 CYTOKINE CLUSTER (IBD5 LOCUS) IN GENETIC SUSCEPTIBILITY TO ULCERATIVE COLITIS AND CROHN’S 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 (IBD5 locus, Rioux et al.,
Nature Genetics 2001). Although the disease gene has not been precisely characterised, the cluster contains the immunoregulatory cytokines IL4, IL5 and IL13 involved in Th1/Th2 responses. The role of the IBDS risk haploidy in ulcerative colitis is unknown.

Aims: (i) To determine, in UK Caucasian cohorts, whether ulcerative colitis is influenced by the 5q31 cytokine cluster risk haploidy, and assess its role in Crohn’s disease (CD).

Methods: A genetic variant (IGR2060a_1), unique to the 250kb CD risk haploidy, was genotyped in 457 families containing 294 CD and 254 UC trios, all UK Caucasian. Family-based (ASPEX transmission disequilibrium test, TDT) association analysis was performed. CD analyses were sub-stratified by NOD2 status (carrier of Arg702Trp, Gly908Arg, Leu1007S1007insC).

Results: No association was seen between the 5q31 risk haploidy and ulcerative colitis (TDT Transmitted/Untransmitted: 105/124, P=0.24). Association was confirmed with Crohn’s disease (162/114, P=0.006), specifically in CD patients not carrying NOD2 mutations [110/67, P=0.003(CD NOD2 carriers, 32/47, P=0.3)]. In the UK population the haploidy plays a lesser role in CD susceptibility than in the Canadian population (1/5 CD 1.4 or CD NOD2neg 1.6 versus CD 2.5; an estimate of genotype relative risk using a multiplicative model).

Conclusion: The 5q31 cytokine cluster risk haploidy does not influence susceptibility to ulcerative colitis and plays a lesser role in genetic susceptibility to Crohn’s disease in the UK than in the Canadian population. In addition, these data provide experimental evidence for genetic heterogeneity in Crohn’s disease.

CD14 and PPARγ Polymorphisms: Candidate Genes for IBD?

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 (LOD λ=1.6) (Duer et al., AGA 2001). PPARγ2 agonists antagonize monocyte function through inhibition of activated protein 1 and NFκB. Trogilizone (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 265

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CD14</th>
<th>Pro12Ala</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>249</td>
<td>265</td>
</tr>
<tr>
<td>UC</td>
<td>113</td>
<td>120</td>
</tr>
<tr>
<td>CD (overall)</td>
<td>131</td>
<td>143</td>
</tr>
<tr>
<td>CD (NOD2+)</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>CD (NOD2-)</td>
<td>88</td>
<td>86</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.

NOD2/CARD15 Mutations in a Scottish Crohn’s Disease Population

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Introduction: Germline mutations in the Nod2/CARD15 gene have been associated with a susceptibility to Crohn’s disease (CD) in North American and European populations but frequency of such mutations in a Scottish population is unknown.

Aim: To assess the frequency of Nod2/CARD15 mutations in a Scottish population and document phenotypic associations.

Methods: Genomic DNA was extracted from venous blood of 215 well characterised patients with inflammatory bowel disease (123 CD and 92 ulcerative colitis (UC)) and 46 healthy controls (HC). PCR based genotyping was carried out using allele specific primers designed to identify the three common single base pair polymorphisms previously described [1007fs, G908R, R702W].

Results: Allelic frequencies for the 3 SMP are displayed in table 1. There were no significant differences between CD, UC, and HC. The frequency of the 1007fs mutation in CD patients in this study differs from previously published data (table 2) whereas that of HC does not.

Conclusions: Results from the present study contrast previously published data. Explanations for this discrepancy may include phenotypic heterogeneity in age of onset, extent of involvement and familial tendency and ethnicity.


Abstract 266, Table 1 Allelic frequencies of Nod2/CARD15 mutations 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>
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<td>131</td>
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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 Allele 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 al1</td>
<td>97/608</td>
<td>9/180</td>
<td>14.314</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hugot et al2</td>
<td>112/936</td>
<td>9/180</td>
<td>7.587</td>
<td>0.006</td>
</tr>
</tbody>
</table>

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.

### Abstract 267

<table>
<thead>
<tr>
<th>EIM</th>
<th>PSC Colitis</th>
<th>UC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>4 (6%)</td>
<td>9 (1%)</td>
<td>0.009</td>
</tr>
<tr>
<td>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.

### Abstract 268

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

S. Ganesan1, S. Iyer2, S.P.L. Travis1, S. Davis1, J. Vogt2, R. Jazrawi1, R.J. Tesi1, R. Beulow. 1Phase 1 Clinical Trials Unit, Plymouth; 2Sangstat Medical Corporation, Fremont, CA; 3Gastroenterology Unit, Oxford, UK

**Introduction:** RDP-58 is a D-isomeric decapeptide that inhibits TNF-α.

**Methods:** Oral RDP-58 is safe and rapidly effective in primate colitis, with a prolonged duration of effect after dosing for 3 weeks.

**Results:** See table. All responses occurred with 1 day of dosing.

**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.

### Abstract 269

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

A.L. Hars1, 2, R. Rigby1, A. Jones1, M.A. Kamm3, 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+ (β7αβ7β) and β7+ populations within CD3+CD45RA- leukocytes 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 healthy samples, fewer β7+ cells from Crohn’s disease patients produced IL-10 but more produced TGFβ.

**Conclusions:** Recruitment to inflamed tissue probably contributes to the observed loss of blood β7+ memory cells in Crohn’s disease. Alterations in cytokine production suggest selective recruitment of functionally distinct populations. These perturbations in β7+ populations support the development of therapeutic strategies that target these cells.

### Abstract 270

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

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

**Background:** Cytochrome P450 enzymes convert many chemicals (including cyclosporin and endogenous corticosteroids) into more water soluble products thereby facilitating their elimination from the body. CYP3A is the most abundantly expressed P450 in the liver. Up to 90% of the inter-individual variation in CYP3A activity is genetic in origin. CYP3A activity is the sum activity of the family of CYP3A genes including CYP3A4. SNPs in CYP3A5*3 cause alternative splicing and protein truncation resulting in the absence of CYP3A5 in tissues. Cyclosporin and corticosteroids are also substrates of the efflux pump P-glycoprotein 170 (Pgp-170) encoded for by the MDR-1 gene. Patients with IBD poorly responsive to medical therapy have increased MDR-1 expression. Recently homozygosity for a polymorphism in exon 26 of MDR-1 has been associated with lower duodenal MDR-1 expression and elevated serum substrate (digoxin) levels.

**Aims:** To evaluate whether carriage of the CYP3A5*3 SNP and the MDR-1 exon 26 polymorphism predict the need for colectomy in patients with ulcerative colitis.

**Methods:** Allele counts were compared between 135 patients with UC who needed colectomy and 182 patients with pan-ulcerative colitis who have not required surgery.

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

**Conclusions:** These polymorphisms do not predict the need for colectomy in UC. Future studies should examine the role of other polymorphisms within genes involved in drug metabolism.
Impaired linear growth is a major complication of Crohn’s disease in young patients. Both undernutrition and direct effects of the inflammatory process contribute to the growth deficit. In the trinitrobenzene (TNBS)-induced colitis model, immunoneutralisation of interleukin-6 increases serum concentrations of insulin-like growth factor-I (IGF-I) and linear growth. Immunoneutralisation of tumour necrosis factor-α (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.

**272 CROHN’S DISEASE AND ULCERATIVE COLITIS: DIVERGENT TRENDS IN HOSPITAL ADMISSION RATES**

D.A.J. Lloyd1, P.J. Neild1, A. Tinto2, A. Majeed3, J.D. Maxwell1, J-Y. Kang1
1St George’s Hospital, London; Office for National Statistics, London; 3University College, London

**Aim:** To investigate time trends in hospital admissions for Crohn’s disease and ulcerative colitis in England from 1989/90 to 1999/00.

**Methods:** Data were obtained from the Hospital Episodes Statistics (HES) service from 1989/90 to 1999/00 based on records of ‘Finished Consultant Episodes’ in England. Hospital admissions were selected by primary diagnosis (ICD 9: 555 and ICD 10: K50 for ulcerative colitis; ICD 9: 556 and ICD 10: K51 for ulcerative colitis) and admissions where a surgical operation, excluding endoscopic procedures, was performed were identified. Day case admissions were excluded. Age standardised hospital admission rates were calculated by comparison with the European standard population.

**Results:** Over the 10 year study period, the admissions rate for ulcerative colitis peaked in 1994/95 and declined thereafter. The proportion of patients undergoing surgery increased by 38% in patients with ulcerative colitis but did not change in patients with Crohn’s disease.

**Conclusions:** Hospital admission rates for Crohn’s disease have risen significantly between 1989/90 and 1999/00, while for ulcerative colitis they have increased only slightly and have been in decline since 1994/5. Increasing proportions of patients with ulcerative colitis, but not Crohn’s disease, are undergoing surgery. Although these 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 INCIDENT OF NON-COMPLIANCE**

S. Webster, D.S. Sanders, L. Lennard, A.J. Lobo. University of Sheffield, Section of Medicine and Pharmacology, Department of Gastroenterology, The Royal Hallamshire Hospital, Sheffield S10 2JF, UK

**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/8x10^12 red cells and the azathioprine dosage from 1.25mg/kg (median 1.6) in the n=89 cohort. Within this group there was no difference in TGN range or azathioprine dosage for patients on monotherapy (n=20), azathioprine and steroids (n=15) or azathioprine and 5-aminosalicylic acids (n=42). There was no significant difference in TGN metabolite concentrations between patients in remission (n=80, median TGN 176 pmol) compared to the small number with active disease (n=9, median TGN 153 pmol).

**Conclusion:** There was a 9 fold range in steady state TGN concentrations between IBD patients in remission. This range was not influenced by constant 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**

P. Kennedy, J. Andreyev, B. Gazzard, J. Fell, I. Murray-Lyon, P. Vlavianos, D. Westaby, R. Zeegen. Chelsea & Westminster Hospital & Imperial College School of Medicine, London, UK

**Background:** The limitations of corticosteroids in the treatment of Crohn’s Disease (CD) are well recognised. About half the patients with CD who initially respond to medical therapy relapse within one year or become dependent on steroids with their associated risk of toxicity. One fifth of patients are unresponsive to steroids and many continue to have refractory disease despite combination therapy with immuno-modulatory drugs. Fultuating CD rarely heals with conventional medical therapy. This underlines the need for an alternative agent in the treatment of active CD. Intestinal mucosal production of TNFα is increased in CD and has a key role in the initiation and propagation of intestinal inflammation. Infliximab (IgG1 chimeric monoclonal antibody) binds soluble and membrane bound TNFα and so acts to neutralise its effect.

**Methods:** We undertook a retrospective analysis of patients treated with Infliximab for refractory CD in our unit. The clinical indications, treatment protocol and outcome of these patients were reviewed. Clinical records, haematological and biochemical indices and where available, endoscopic and histological findings were recorded 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 fluctuating CD (n=5) and refractory luminal CD (n=14). 11/19 had undergone previous SI surgery. 18/19 were unresponsive to and intolerant of steroids. 13/19 had failed to respond to at least 1 immuno-modulatory drug. Infliximab (5mg/kg) was administered by infusion over 2 hours with intravenous steroid and 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 previously recorded no side effects were reported. 14/17 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 fistulating CD.

**DRB1*15 MOLECULAR SUBtyping CONFIRMS THAT CAUCASIAN ULCERATIVE COLITIS (UC) IS ASSOCIATED WITH DRB1*1502 AND NOT DRB1*1501**

T. Ahmed, M. Bunce, K. Mulcahy-Hawes, A. Armuzzi, J. Crawshaw, O. Large, K. Welsh, D. Jewell. Departments of Gastroenterology, Transplant Immunology, University of Oxford; National Heart and Lung Institute, Imperial College, London, UK

**Background:** A replicated association between UC and the serotype DR2 has been reported in the Japanese. Studies in caucasian populations however have produced more conflicting results. Modern molecular typing has shown that the Japanese association is attributable to DRB1*1502, an allele common in this ethnic group but rare in Caucasians. This allele differs from DRB1*1501 by a single amino acid (position 86 of exon 2), located within pocket 1, which may alter peptide binding. DRB1*15 molecular subtyping has been carried out in 5 previous studies of Caucasian patients. Only one (Tra- chtenberg et alHum. 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 caucasian 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:** DRB1*1502 was associated with disease susceptibility (4.2% vs. 0.8%; P=0.004; RR 4.59; CI 1.31–16.11). A rare extended haplotype A*3201-Cw*1202-B*5201-MICA*00901-MICB*0102-IC7H3-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 or severity, but 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 (CACRN)**

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Persistent colonic inflammation in ulcerative (UC) and Crohn’s colitis (CD) confers increased colorectal cancer risk. Tumour necrosis factor alpha [TNFα] mediates inflammation in colitis. TNFα promoter polymorphisms associated with variable TNFα production. This study tests the hypothesis that TNFα promoter polymorphisms confer cancer risk, in colitis.
DIFFERENCES IN MICRO-VASCULAR BLOOD FLOW AT SITES OF SKIN BISTERNING MAY ACCOUNT FOR REDUCED LEUKOCYTE TRAFFICKING IN CROHN’S DISEASE

R. Day, M. Harbord, A. Segal, A. Forbes

Background and Aims: Previous studies have demonstrated a reduction in the number of neutrophils migrating into skin windows in patients with Crohn’s disease (CD). This effect may result from an impaired 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. Blister tissues were collected at 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 skin blister at 24 h was lower in the control group (mean ± SEM; CD: 4.23x10^6 ± 1.630 cells/ml; controls 5.68x10^6 ± 1.644 cells/ml). Micro-vascular blood flow was significantly decreased at both 8 h and 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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<table>
<thead>
<tr>
<th>Organ</th>
<th>Normal</th>
<th>CD</th>
<th>P value</th>
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<tbody>
<tr>
<td>8 h</td>
<td>103.7 (45.18)</td>
<td>257.9 (47.53)</td>
<td>0.0358</td>
</tr>
<tr>
<td>24 h</td>
<td>310.5 (51.18)</td>
<td>237.0 (55.06)</td>
<td>0.1825</td>
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Conclusion: Reduced neutrophil migration into CD skin windows may be caused by inappropriate changes to micro-vascular blood flow. This could result from either a leukocyte or endothelial cell defect leading to impaired diapedesis of cells from the vascular lumen into the surrounding tissue. A defect in innate immunity such as this could account for some cases of inflammatory bowel disease.

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 polyposis progression, hence an alternative molecular pathway is thought to exist. Activation of phosphoinositide-3-kinase gamma (PI(3)K gamma) leads to altered cell activation, growth and apoptosis. Mice deficient in PI(3)K gamma develop ulcerative colitis and adenocarcinoma. The PTEN tumour suppressor gene opposes the action of PI(3)K gamma and mice deficient in PTEN develop tumours and autoimmune phenomena. We therefore hypothesised that abnormal PI(3)K gamma signalling may contribute to the development of CRC in patients with IBD.

Method: Expression of PI(3)K gamma 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 P(3)K gamma 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 P(3)K gamma or PTEN in sporadic CRC when compared with normal tissue.

Conclusion: Loss of expression of P(3)K gamma and PTEN proteins is common in IBD associated CRC. We conclude that aberrant signalling through this pathway may occur in IBD associated CRC.
ADENOMATOUS POLyps ARE RARE IN ULCERATIVE COLITIS

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Colon cancer in ulcerative colitis (UC) does not follow the adenoma-carcinoma sequence of non-UC colorectal neoplasia. Polyps with dysplasia do occur in UC, and there is debate whether they should always be managed as dysplasia associated lesion/masses (DALMs) requiring colectomy, or whether some can be managed as sporadic adenomas by polypectomy. There are few data on the prevalence of non-inflammatory polyps in UC; this study aimed to see if adenomatous polyps occur as often in UC as in patients without inflammatory bowel disease (IBD).

The clinical, endoscopy and histology records of 150 patients with UC undergoing colonoscopy were scrutinised for any history of polyps. The control group was 205 patients having colonoscopy for altered bowel habit. Patients with rectal bleeding, anemia, abnormal barium enema, a personal or family history of colorectal cancer or polyps 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 not 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) disease 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 12 (8%). Only 6 UC patients had ever had dysplastic polyps. 2 had a single adenomatous polyp proximal to the colitis segment. 4 patients had dysplastic polyps within the colitis segment. In 2 of these the polyps were treated endoscopically as sporadic adenomatous polyps (1 patient having 2 polyps). In the other 2, the lesions were considered to be DALMs and colectomy advised. In contrast, 24 controls had at least 1 adenomatous polyp, \( \chi^2 = 6.7 \), p<0.01. Metaplastic polyps were found in 4 UC patients (within colitis in 3, proximal to colitis in 1) and in 24 control patients, \( \chi^2 = 9.7 \), p<0.01. 38 UC patients had inflammatory pseudopolyps.

Adenomatous and metaplastic polyps occur less frequently in patients with UC than in patients without IBD. Despite the increased cancer risk in longstanding UC, the colitic mucosa (or possibly drug treatment of UC) seems to protect against the formation of sporadic adenomas.

MAGNETIC RESONANCE IMAGING (MRI) IN PATIENTS WITH ACUTE COLITIS: A PILOT STUDY

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Aim: To evaluate the potential of MRI in patients with acute colitis.

Methods: Consecutive patients admitted with acute colitis were studied. All had AXR on admission and MRI of the colon. Axial (T1/ T2) and sagittal T1 images were performed according to a predetermined protocol using a Siemens 1.5 Tesla Vision Scanner. The following parameters on AXR were recorded: disease extent, bowel dilatation and wall thickness. At MRI, disease extent, bowel dilatation, wall thickness, changes in peri-colic fat and the presence or absence of free fluid were noted.

Results: To date eleven patients with acute colitis have been included. One male and ten females, mean age 40.7 (range 22–71) were analysed. Six out of eleven patients with Powell Tuck score ranging between 8–13 had no or minimal changes on AXR. MRI showed disease extent and established bowel wall thickening in all six cases. Three patients required colectomy and in two of these cases MRI showed free fluid and changes in peri-colic fat.

Conclusions: (1) MRI is more informative than a plain abdominal film in assessing the severity and extent of disease in patients admitted with acute colitis. (2) Features like presence of free fluid and changes in the peri-colic fat may be important prognostic factors.
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.

287 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: 23,623 men and women aged 45–74 years in Norfolk, UK (the EPIC Norfolk study) and 3,145 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=0.7–11.1], sugar OR=1.8 [95% CI=0.5–7.3], fat OR=1.6 [95% CI=0.5–5.6]). A higher fish consumption appeared to protect against the development of ulcerative colitis (lower vs middle tertiles OR=0.5 [95% CI=0.1–2.1] & lower vs upper tertile OR=0.8 [95% CI=0.2–3.2]).

Conclusions: A prospective cohort study of diet and ulcerative colitis is feasible. Other European centres participating in EPIC now need to be included to increase the number of participants studied so that the role of diet in the aetiology of ulcerative colitis can be accurately defined.

288 COMPLIANCE WITH MAINTENANCE MESALAZINE IN INFLAMMATORY BOWEL DISEASE

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Background: Most patients with inflammatory bowel disease are prescribed regular medications to reduce the risk of disease relapse. Non-compliance with such treatments may increase the risk of relapse and some have suggested an increased risk of colorectal cancer. We have therefore conducted a survey of outpatients with IBD to determine the prevalence of non-compliance with maintenance mesalazine therapy, and to identify possible risk factors.

Methods: Outpatients with quiescent IBD receiving maintenance therapy with delayed-release mesalazine (Asacol) were recruited to the study. Patients underwent a structured interview including assessment of 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 (0.4–4.3) g/day for 4.3 (0.2–13) years. 64% of patients were prescribed mesalazine three times daily. A discrete NSAID stricture. These 4 are termed alternative group (AG).

Conclusions: A higher prevalence of non-compliance with maintenance mesalazine therapy has been demonstrated. This 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.

289 RELATIONSHIP OF THIOPURINE METHYLTRANSFERASE (TPMT) ACTIVITY TO MEAN CORPUSCULAR VOLUME (MCV) IN INFLAMMATORY BOWEL DISEASE (IBD) PATIENTS MAINTAINED ON AZATHIOPRINE

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Introduction: TPMT is a cytosolic enzyme that catalyses the S-methylation of aromatic and heterocyclic sulphhydril compounds including 6-mercaptopurine and azathioprine (AZA). AZA induces TPMT activity variably and unpredictably. We have recently reported that IBD patients with TPMT activity > 20 nmol/hr/ml of RBC relapse more often if AZA is prescribed at doses < 2 mg/kg/day. MCV is increased in patients on AZA, but the implications of this increase in guiding AZA therapy is unclear. We investigated the relationship between TPMT activity and MCV in IBD patients 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/hr/ml of RBC compared with MCV of 92.19 fl (SD 5.77) in patients with TPMT > 20 nmol/hr/ml of RBC (p = NS). A Kaplan-Meier survival curve was constructed based on time to first relapse for patients with MCV ≤ 98 fl compared with MCV > 98 fl and the difference was not significant by log rank analysis.

Conclusions: In IBD patients on AZA, MCV does not correlate with TPMT activity. MCV in IBD is influenced by a number of conflicting factors such as iron or folate deficiency, and cannot be used to determine AZA effect or outcome of therapy.

290 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. 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 responded to each of antibiotics, IBD therapy or resection with spontaneous remission in the remainder. Histological appearances of resection specimens and biopsies revealed nothing characteristically to distinguish PPI from pouchitis.

Conclusion: 15 cases of pre-pouch ileitis were found in patients with confirmed UC and otherwise normal BAFT with no histological evidence of Crohn’s. This disease may have a distinct pathogenesis from Crohn’s.
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 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 table1).

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 TNFa antibody, Infliximab offers an alternative to current medical therapy in CD with two thirds of treated patients responding. There are however concerns regarding potential immunogenic and immunosuppressive effects. TNF 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 TNFA and lymphotoxin alpha (LTA) genes can predict response to Infliximab.

Methods: 3 LTA (+A720C, +C365G and +G249A) and 7 TNFa (Taq1, Fok1, Apa1, –1031C, –863A, –857A, –308A and –308G) polymorphisms were genotyped by PCR-SSP in two patient cohorts.

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: 141 patients with UC, 71 with CD and 178 healthy controls were genotyped for TNF-1031C and LTA-863A. The ‘f’ allele was associated with extensive colitis in both UC and CD.

Conclusions: The polymorphisms studied in the TNFA and LTA genes do not predict response to Infliximab. The association with TNF-1031C observed in Stage 1 is likely to represent a Type 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 vitamin D, 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. All patients were genotyped for the 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 (‘r’ allele) were increased in CD patients (31%) vs control (12%), p=0.001. The Fok1 ‘f’ allele was associated with extensive colitis in both UC and CD.

Conclusions: The Taq1 ‘r’ genotype is associated with CD. The Fok1 ‘f’ 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 between January 2001 and January 2002 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, Age 44 years). The overall prevalence of bacterial translocation was 19% (12/64 patients). The most commonly isolated organism from nodes and serosa was Escherichia Coli (42%). Twelve patients (19%) developed 14 septic complications. Enteric organisms were responsible in 86%. Patients with microbiological evidence of BT had a higher incidence of postoperative sepsis (4/12, 33% vs 8/52, 15%, P = 0.15).

Conclusions: Bacterial translocation occurs in patients with IBD and may promote the development of septic morbidity. Our data supports the gut origin of sepsis hypothesis.
**TGF-β1 EXPRESSION IS UPREGULATED IN CROHN’S DISEASE (CD) BUT NOT IN ULCEARTIVE 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-β1 results in upregulation of mucosal expression of TGF-β1 in IBD tissues compared with ED alone.

**Method:** Three liquid formulae were used: (1) ED (EO28, SHS Ltd, Liverpool) with addition of bovine colostrum rich in TGF-β (0.9mg TGF-β per 100gm colostrum) (ECO); (2) ED with addition of whey enriched with TGF-β1 (300mg TGF-β1 per 1gm whey) (EWT); (3) ED alone. Colonoscopy biopsies from patients with CD (n=23), UC (n=13) and non-inflamed controls (n=19) were incubated for 24h in Waymouth medium diluted 1:20; 1:10 and 1:5 with ECO, EWT and ED alone as control. Tissue viability was determined by BrdU uptake. Immunohistochemical staining was performed for TGF-β1 with a polyclonal rabbit anti TGF-β1 (Santa Cruz Biotechnology, sc-146, UK) diluted 1/50 in 20 % Normal sheep serum (diluted in 0.05 molar TBS, pH 7.6). Cryostat and epithelial surface staining was quantified with a Video-Image-Analyzer Q500MC (Leica Cambridge, UK) examined under a calibrated x 10 objective. Results are expressed as % of staining expression per mm of tissue (mean ± SEM) and compared with one-way ANOVA.

**Conclusion:** Incubation of CD tissue with ECO alone resulted in a significant increase in TGF-β1 expression in all 3 dilutions: 1:20 (43.87±3.19, p<0.0001), 1:10 (27.35±7.13, p<0.0001), 1:5 (29.4±14.0, p=0.09) compared with control medium alone (3.57±0.6). EWT incubation resulted in a similar increase in TGF-β1 expression: 1:20 (32.87±5.78, p<0.0001), 1:10 (28.1±11.4, p<0.001), 1:5 (33.1±11.8, 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.

**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 bowel disease. YKL-40 is a member of the chitinase family of enzymes. It is synthesized by human macrophages and is released into the circulation during tissue repair processes. In the intestinal mucosa, YKL-40 is induced by the cytokines interleukin-1 and tumor necrosis factor-alpha. The percentage of inflammatory infiltrate occupied by macrophages were: 6.3±0.4 vs. 5±0.3 in Crohn’s, UC and controls. The area [%±SE] of mucosa occupied by macrophages were: 6.3±0.3 vs. 4.2±0.2 vs. 2.4±0.1 in CD, UC and controls.

**Conclusion:** We have confirmed the presence of Ti, Al and Si 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 microparticles-laden macrophages were (means±SE): 70.4 % vs. 50.5 % vs. ±1.3 in Crohn’s, UC and controls. The area [%±SE] of mucosa occupied by macrophages were: 6.3±0.3 vs. 4.2±0.2 vs. 2.4±0.1 in CD, UC and controls.

**Conclusion:** In UC and control tissues, no significant increase in TGF-β1 expression was observed after incubation with ECO and EWT. Higher levels of YKL-40 were observed only in the active phase 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 in CD patients compared to non or ex-smokers (69.9 vs 103.6 & 102.9 ng/ml respectively).

**CONCLUSIONS:** Serum levels of YKL-40 are increased in patients with inflammatory bowel disease and this is associated with the inflammatory process rather than with the degree of fibrosis.

**DETECTION OF CHROMIUM MICROPARTICLES IN INFLAMMATORY BOWEL DISEASE (IBD) TISSUES BY ENERGY DISPERSIVE ANALYSIS OF X-RAYS**

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**Introduction:** Inorganic microparticles as compounds of titanium (Ti), silicon (Si), and aluminium (Al) have been implicated in pathogenesis of chronic inflammatory bowel disease such as Crohn’s disease (CD) and benefit of reducing intake of such microparticles has been demonstrated in humans. However, the pro-inflammatory roles of Al, Si and Ti are unclear. Other elements such as chromium are more 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 Al, Si and number of microparticles with inorganic microparticles were quantitated by automated image analysis. Specimens were also prepared for EDAX and analysed in conjunction with a transmission electron microscopy. Selected intestinal tissues were from Crohn’s disease, UC and controls [proximal end of cancer bowel].

**Results:** Immunolabelled, CD68+ 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 % vs. 50.5 % vs. ±1.3 in Crohn’s, UC and controls. The area [%±SE] of chromium by EDAX were: 6.3±0.3 vs. 4.2±0.2 vs. 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.

**PATHOGENESIS OF INCREASED BONE TURNOVER IN INTESTINAL INFLAMMATION**

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**Background:** Inflammatory 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) paired (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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299 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 (IBSFD), whilst 45 (58%) of patients with FD had co-existent IBS (FDIBS). Patients with IBSFD reported a greater number of EI symptoms [20(19,22)] compared with IBS only [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 IBSFD had a poorer QOL [28(24.5,31.2)] than those with FD [35.2(31.9,38.4); p=0.02] or not compared with those with FDIBS [32.4(29.3,35.6)] 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 [IBSFD r=0.562, FDIBS r=0.582, IBS r=0.568, FD r=0.469; p<0.01]. Furthermore, FGID symptom severity correlated with both the number of EI symptoms and poor QOL in patients with IBSFD [r=0.573, p<0.001; r=0.333, p=0.017, respectively], FDIBS [r=0.309, p=0.039; r=0.352, p=0.019] and IBS [r=0.392, p=0.035; r=0.333, 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.


Gut: first published as 10.1136/gut.50.suppl_2.a1 on 1 April 2002. Downloaded from http://gut.bmj.com/ on September 22, 2023 by guest. Protected by copyright.
Results: In the subjects who had developed functional diarrhoea or IBS, none had evidence of lactase 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 antacids, lactase 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 lactase intolerance. Lactase 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 lactase intolerance is unfounded.

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 during the processing of 5-HT. There is also evidence that 5-HT levels increase after the ingestion of food and that this may be related to postprandial increase in symptoms.

Methods: Male and female Wistar rats were fed standard rat chow or starved for 24 h (200 g, total n = 24, six in each group). The rats were sacrificed by cervical dislocation and the GITs dissected out and frozen sections immediately in liquid N. 5-HT in the GITs were divided into stomach, small bowel, proximal and distal colon. Frozen sections were weighed and fragmented using a mortar and pestle and a weighed portion placed in 1 ml of 10% v/v perchloric acid (PCA). PCA samples were homogenised using an ultraturrax and spun at 13,000 rpm for 15 min. The resulting supernatant was analysed by HPLC with fluorimetric detection. The results were expressed as concentration of 5-HT in each segment by pmol/mg tissue.

Results: No differences were detected between fed and female 5-HT concentrations in the GIT but fed rats had significantly less 5-HT in the stomach than fasted rats (mean 78.7 ± pmol/mg (lower 95% CL 65.4–upper 95% CL 92.1) vs mean 142.9 pmol/mg (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 males (mean 80.1 ± pmol/mg (CL 60.3–99.8) vs 156.2 (CL 83.1–229.0) p = 0.041).

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

SMOOTH MUSCLE CELL CHOLINERGIC DENERVATION HYPERSENSIVITY 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 cholinergic activity, together with an immunohistochemical 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. Controls: 0.4–55, median 17). Longitudinal muscle showed a reduction in ChAT activity (DD: range 90, median 45. Controls 30–100%, median 95), an up-regulation of M3 receptors (DD: 2–32, median 10. Controls: 1–5, median 2) and increased sensitivity to exogenous acetyl choline (DD: EC50 range 0.3–9.5μmol, median 4. 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 that has not previously been reported in association with smooth muscle.

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 endpoints 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.

COMMUNITY BASED “VOLUNTEERS” WITH IRRITABLE BOWEL 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 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...
The effects of calcium polycarbophil on colonic transit in patients with irritable bowel syndrome.

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 cards 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. Mean colonic transit was 3.2 ± 0.4 hr (p<0.05) before administration of calcium polycarbophil, 35.4 ± 3.3 hr (p<0.05) at 50mls qds for 1 month. Subjects were interviewed at 0, 1 and 3 months. The IBS questionnaire of Whorwell (APT 1997) was used to detect change in symptoms. The primary endpoint was a response to a fat rich meal as compared to a carbohydrate rich meal.

Results: Diarrhoea type: Mean colonic transits were 3.2 ± 2.9 hr (p<0.05) before administration of calcium polycarbophil, 10.4 ± 3.2 hr after administration (p<0.05). Bowel movements were 3.2 ± 0.6 times/day before administration (p<0.05). The Bristle 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 ± 3.2 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 Bristle 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.

The effects of calcium polycarbophil on colonic transit in IBS patients and healthy controls. Bowel movements and stool type were improved.

Methods: In IBS patients, the MI and freq were consistently lower in the postprandial period as compared to controls. These differences were significant throughout the postprandial period, but freq difference was not significant (p<0.05).

Results: 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.

Calcium polycarbophil is useful for improving abdominal symptoms in patients with irritable bowel syndrome.

The effect of protein, carbohydrate and fat rich isocarbo meal on postprandial small bowel motility in irritable bowel syndrome (IBS) patients.

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 isocarbo meal in IBS patients and healthy controls.

Methods: 19 IBS patients (22M/17F) 10 constipation predominant (C-IBS), 9 diarrhoea predominant (D-IBS) and 4 healthy controls (6M/4F) were studied. Ambulant small bowel motility was measured using a solid-state flexible catheter positioned in the proximal jejunum. Each subject ingested the three isocarbo test meals (high fat, high protein and carbohydrate) in a random order. Automated data analysis was performed using a validated software program. The postprandial motility index (MI) and contractile frequency (freq) were calculated for two 60-minute epochs.

Results: In D-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.
Does illness perception of bacterial gastro-enteritis differ in people with a functional gastrointestinal disorder (FGID) and can it predict who will go on to develop a post infectious FGID?

S.D. Parry, S. Corbett, P. James, J.R. Barton, M.R. Welfare.

Background: IBS can develop after gastro-enteritis. Cognitive factors (such as illness representation) may be important influences on the development of post-infectious IBS but have not been extensively studied.

Aims: Do differences exist in illness perception in people with recent stool culture positive bacterial gastro-enteritis with and without a prior FGID and also in those who go onto develop a FGID compared with those who do not.

Methods: 217 people with recent bacterial gastro-enteritis completed a postal gastro-intestinal disease questionnaire (GIDQ) incorporating the Rome II modular questions relating to IBS, functional dyspepsia or functional diarrhoea asking about symptoms during the last year. The cases were divided into those with (n=82) and without a prior FGID (n=122). All cases then completed the Illness Perception Questionnaire (IPQ-Weinman et al.), which taps into 5 areas of illness perception: Cause, identity, timeline, consequences and control/cure. Those without a prior FGID were followed up and a similar GIDQ was completed at six months. 25 people subsequently developed a FGID and 82 did not.

Results: People with a prior FGID had significantly more symptoms (identity domain) and scored significantly higher on the timeline and consequence scores than those without. People who developed a FGID had higher consequence scores than those who did not and a non-significantly higher number of symptoms. Neither comparative group differed in the control/cure scores or causation scores.

Conclusions: People with recent bacterial gastro-enteritis and a prior FGID have more symptoms relating to their gastro-enteritis, think their illness will last longer and is more serious than those without a prior FGID. People who develop a post-infectious FGID tend to believe their gastro-enteritis is more serious than those who do not. We conclude therefore that having a FGID influences a person’s perception of bacterial gastro-enteritis. However, illness perception is not a strong predictor for the subsequent development of a FGID.

Gender differences and effects of age on 5-hydroxytryptamine (5-HT) turnover: implications for irritative bowel syndrome (IBS)


Irritable bowel syndrome (IBS) is more common in women than men, suggesting that they may have a predisposition to the condition. As recent studies have suggested that 5-HT may play a role in the aetiology of IBS, we investigated whether fasting platelet depleted plasma 5-HT and its metabolite, 5-hydroxyindole acetic acid (5-HIAA), and platelet 5-HT concentrations are different between healthy males (n=22; aged 21–63 yrs) and females (n=22; aged 22–63 yrs). The effect of increasing age on fasting 5-HT and 5-HIAA concentrations was also assessed. 5-HT and 5-HIAA concentrations were measured by a reverse-phase high performance liquid chromatography (HPLC) with fluorometric detection.

Results: Healthy females had similar concentrations of both fasting platelet and plasma 5-HT (platelet: 603ng/10^9 platelets (343,863ng/10^9 platelets) respectively of subjects were followed to 1 month and 6/27(60%) and 25/32(78%) for 3 months. 72% and 91% had diarrhoea predominant or mixed IBS. 10/22(45%) in the placebo and 18/27(67%) in the active group showed a response to treatment at 1 month (p=0.13). There was no difference by 3 months. There was significant improvement in pain score at 3 months (p=0.05). In the diarrhoea and mixed bowel habit subgroup, there was a trend towards an improvement in IBS score at 1 month, 44% v 67% improving (p=0.15), a significant improvement in the proportion of subjects with any pain in the past week p=0.046, a trend towards an improvement in the % of days without pain in the past week (p=0.06), and in satisfaction with bowel habit p=0.06. By 3 months these changes had disappeared.

Conclusion: In this study of resistant IBS, there was some evidence of efficacy for the IBSCOL formulation of Aloe Vera that was well tolerated. These findings require replication in a larger, and milder group of patients.

Modulation of the human swallowing mechanism by thermal and chemical stimulation in health and after brain injury

S. Hamdy, S. Jilani, V. Price, N. Hall, M. Power (introduced by D.G. Thompson). Department of GI Sciences, Hope Hospital, Eccles Old Road, Salford M6 8HD, UK

Background/Aims: Swallowing is a complex neuromuscular activity dependent on sensory feedback. Following stroke, dysphagia is commonly treated by sensory stimulation techniques including thermal and chemical stimulation. However, little data support the use of such methods to favourably alter swallowing 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: Healthly volunteers (n=65, mean age 45 yrs, 25 male, 40 female) and acute (72hrs) stroke patients (n=12, mean age 61.3yrs, 4 male, 8 female) admitted to a stroke rehabilitation unit were studied. A bedside timed 50 ml water-swallowing test was performed in a randomised manner at a) room temperature (RT), b) cold (4°C) (CD), c) 5% citrus (CT) and d) combined cold and citrus (CD+CT). The time taken to swallow (speed), and the number of swallows (capacity) per volume were measured with each condition on 3 occasions. Comparisons between each condition were made with ANOVA.

Results: In health, whilst both CD and CT alone showed a trend towards altering the swallow, compared to RT water, only combined CD+CT slowed the speed (10.3 vs. 11.3 ml/s, p<0.01) and the capacity (14.6 vs. 16.4 ml/swallow, p<0.01) of swallowing. A sub-analysis, based on age showed that this effect was present both in the young (<60yrs) and old (>60yrs) alike. When applied to stroke, compared to RT, CD+CT slowed both the speed (5.0 vs. 6.1 ml/s, p<0.06) and capacity (9.7 vs. 11.1 ml/swallow, p=0.05) of swallowing.

Conclusions: Combining thermal and chemical sensory modalities to water boluses can substantially alter the pattern of normal swallowing in health and after stroke. The ability to slow and reduce the amount of volume taken per swallow may be advantageous in patients with dysphagia where inappropriately judged bolus intake is a factor in the development of aspiration.
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313 DOES IMPLEMENTATION OF ANTIBIOTIC PROPHYLAXIS IN PEG INSERTION AFFECT INCIDENCE OF WOUND INFECTION?

V. Christopher, S.D. Hearing, J. Smithson, S. Hughes. Dept Gastroenterology, Southmead Hospital, Bristol, UK

Percutaneous gastrostomy (PEG) insertion is associated with a significant morbidity. Recent studies suggest that antibiotics given at the time of PEG insertion may reduce complications, in particular soft tissue infection. A previous audit of all PEGs from Feb 1998 to July 1999 performed in our unit revealed a high rate of PEG site infection, although most cases were not severe (14.2%). A policy of prophylactic antibiotics (Ampicillin 1g IV, Gentamicin 80mg IV) administered at the time of PEG insertion was instituted and complication rate was reduced.

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 15.3), range 36–98, M:F =27:22. Indications for PEG: CV/CNS disorders =27, neoplasia =12, 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.

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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%), 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 ZAMBIA 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% marasmin-kwashiorkor. Weight gain was greater in the Neocate group (median gain in weight-for-age z score 1.23, interquartile range 0.89 - 1.57) compared to Control (0.87, 0.47 - 1.25; p=0.002), despite greater calorie intakes in the Control group. Increase in haemoglobin concentration was also greater in the Neocate group (0.8g/dl, 0 - 1.8) than the Control group (0.3, 0.6 - 1.6; p=0.04). Diarrhoea frequency and global recovery scores improved equally in both treatment groups. Mortality was higher in HIV seropositive children and those with cryptosporidiosis, but did not differ between treatment groups.

Conclusions: Exclusive use of an elemental diet for 4 weeks was associated with significantly improved nutritional recovery in children with severe PDM, irrespective of HIV infection.

316 PERCU TANEOUS ENDOSCOPIC GASTROSTOMY: PROSPECTIVE CLINICIAN REVIEW APPROPRIATELY DECREASES INSERTION

A.I. Thuraisingam, S.A. Cairns. Royal Preston Hospital, Preston PR2 9HT, UK

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 dietitian 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. Teeshan. 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 parenteral feeding prior to NJT feeding. The commonest indications for the use of NJT feeding were reduced oral intake during chemotherapy (24 patients), gastric-oesophageal malignancy (14), prolonged or complicated post-operative recovery (14), acute pancreatitis (12), benign gastro-intestinal disease (10) and severe burns (10). 96 patients had an NJT successfully placed and in 88 nutritional requirements were successfully met. NJT feeding was continued for a median of 11 days (range 0–180 days). 65 patients were discharged home, 30 died as an in-patient and 7 were discharged to another hospital. 11 patients had NJ feeding continued at home. In 37 patients, medication was given by the NJT. There was one serious complication of a significant small bowel bleed possibly caused by NSAIDs given down the NJT. Minor complications included NJT displacement necessitating replacement (13), diarrhoea (6) and blocked NJT (4). 1 patient had small bowel obstruction that appeared to be related to their underlying malignancy.

Conclusions: NJT feeding can successfully and safely meet nutritional requirements of many critically ill patients. Patients with gastric stasis or vomiting, such as patients undergoing chemotherapy, with severe burns, prolonged or complicated post-operative recovery or with acute pancreatitis, can be successfully fed nasojejunally. There may be cost savings related to reducing the demand for parenteral nutrition.

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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.

THE SHORT TERM EFFECTS OF TOTAL PARENTERAL NUTRITION (TPN) ON FATIGUE: A DOUBLE BLIND PLACEBO CONTROLLED STUDY

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Aim: We wanted to know if the feeling that some patients report of feeling better soon after starting TPN was real or due to placebo.

Methods: Design: Prospective 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 methods, energy and water. Water, Na, and K infusion, and placebo do not account for this effect

Biopsies were performed. Of these, 50% (28) of the patients needed 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 additional information around the tumour leading to incorrect staging. However we found that the overall intra and inter observer agreement using hard copies is good.

RADIOLoGY POSTERS 321-325

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 sitting. Then the biopsy was performed using the most appropriate site, away from potential structures that can be encountered in the biopsy needle path.

Results: All patients preferred to have US guided biopsy when they were offered a choice between blind and US guided biopsy. Liver biopsies were performed. Of these, 50% (28) of the patients needed additional information around the tumour leading to incorrect staging. However we found that the overall intra and inter observer agreement using hard copies is good.

Aim: 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, surgeon 1 (S 1), ’T’ staged 16 out of 31 cancers accurately (K = 0.46) and surgeon 2 (S 2), ’T’ staged 7 out of 31 accurately (K = 0.34). Radiologist 1 (R 1), ’T’ staged 14 out of 31 cancers accurately (K = 0.242) and radiologist 2 (R 2), ’T’ staged 15 out of 31 cancers (K = 0.302). (R 1) had an excellent intraobserver agreement in ’T’ staging (K = 0.792) and (R 2) a perfect intraobserver agreement (K = 1) compared to their original preoperative staging. Between R1 and R2 interobserver agreement was good (K = 0.681). Between (S1) and (S2) interobserver agreement was moderate (K = 0.46) and between R1 and S1 agreement was good (K = 0.53). The intra and interobserver agreement for nodal ’N’ staging were very similar to the ’T’ staging.

Conclusion: Endorectal ultrasound has been shown previously to be the most accurate method of staging to assess local invasion in rectal cancer. This study does not confirm that observation and it may be due to hard copies used rather than real time images and inflammatory reaction around the tumour leading to incorrect staging.

Aim: 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 oesophagogastrectomy. Enteral Wall stents were used in the remainder of cases (Boston Scientific Int.). The technical success rate was 12/14 (86%). 1 patient required 2 stents and one 3 stents. 3 patients required metal biliary stents. There were no immediate complications. There were no cases of stent migration. 1 patient died unexpectedly within 24 hours of stent insertion. Symptom relief was obtained in the remaining 11 patients. 3 patients survived one week, all succumbing as inpatients to metastatic disease. 8 patients were discharged from hospital. 6 patients survived between 11 and 135 days (mean 35 days) and 2 are still alive at 2 and 4 months. The 2 patients who could not be stented survived 11 and 21 days.

Conclusions: This series demonstrates the effectiveness of enteral stenting in the palliation of malignant obstruction of the upper GI tract, enabling many patients to be supported out of hospital. Improved patient selection will optimise palliation. The preferred method of placement was a combined 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.

Aim: To assess the clinical usefulness of this technique in screening individuals for colonic lesions, locating anomalies projecting from the colonic mucosa and determining their position.

Methods: 283 UK coeliacs were typed for the presence of the DQ2 genotype (DQA1*0501 DQB1*0201) heterodimer encoded in 11% of the UK coeliac population. We report the findings of this study in 283 UK coeliacs, and also to describe HLA types of the rare DQ2 and DQ8 negative coeliacs.

Results: 263/283 (93%) were DQ2 positive (252 in cis, 11 in trans), 20/283 (7%) were DQ2 negative. 15/20 of these were DQ8 negative (75%). 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.

Conclusion: 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 DQ8 positive. 40% of DQ8 haplotypes in DQ2 negative coeliacs carried the DRB1*04 allele, 30% the 0401 allele, 15% each 0402 and 0404 respectively. Of the 5 DQ2 and DK4 DQ8 negative coeliacs, 4 carried one half of the DQA1*0501, DQB1*0201 heterodimer.

Conclusion: There has been a large increase in new cases of coeliac disease in South Glamorgan over the last quinquennium. 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.
HYPOSPLENISM IN COELIAC DISEASE: IS PROPHYLAXIS NEEDED IN SOUTH ASIAN COELIACS RESIDENT IN BRITAIN?

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Background: It is recognised that coeliac disease and ulcerative colitis are associated with hypoplasoin the UK. As severe pneumococcal disease has been increasingly recognised among South Asians resident in the UK, no studies have compared the HLA haplotypes amongst Caucasian and South Asian CD patients.

Methods: A questionnaire was posted to 292 UK gastroenterologists, three months later the results were collated and analysed.

Results: The response rate was 78% (n=229). Coeliac disease: Only 25% (11%) of respondents prescribe pneumococcal prophylaxis for hyposplenism in coeliac disease. Of these 25%, the majority (17%) use pneumovax. To select patients for treatment 22 respondents use haematological indices, two others use ultrasound for this purpose. Of the 229 who responded 9% (n=18) had encountered severe infections in coeliac patients and reported a total 36 severe infections. Severe pneumococcal septicaemia and coexisting immunocompromise were commented on as distinguishing features. Ulcerative colitis: 6% (n=13) of respondents assess ulcerative colitis patients for hyposplenism. Five of these do not treat this hyposplenism.

Conclusions: Despite the suggestions of the Drugs and Therapeutics Bulletins and the British Haematology Guidelines, our findings suggest that current practice is not to assess or treat coeliac patients for hypoplasoin the UK. As severe pneumococcal disease has been encountered, we believe that gastroenterologists should reassess this practice and produce guidance for these patients.

329 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 European populations, however the precise aetiological polymorphism is still not known. CD is associated with other 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).

Aims: To test for association of MH30 and CT60 with CD.

Method: 149 family trios consisting of an affected individual plus both parents were genotyped for both polymorphisms. TDT compares allele transmissions from heterozygous parents to unaffected offspring. For MH30 G=70, C=05 (chi-squared=0.185, 1df, p=0.667), for CT60 G=77, A=67 (chi-squared=0.694, 1df, p=0.403). Similar allele frequencies were demonstrated in case and control groups for both MH30 (chi-squared=0.016, 1df, p=0.899) and CT60 (chi-squared=0.146, 1df, p=0.702). Genotype frequencies were also almost identical in both case and control groups.

Conclusion: Although CD, T1D and GD have all demonstrated association with the CTLA-4/CD28 gene region, the polymorphisms(s) on 2q33 that confer susceptibility to CD may be different from those conferring susceptibility to T1D and GD.

330 SOUTH ASIAN COELIACS RESIDENT IN BRITAIN POSSESS DISTINCT HLA HAPLOTYPES COMPARED WITH WHITE CAUCASIAN 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 CD patients with CD.

Aims: To compare the HLA haplotypes of Caucasian and South Asian CD patients.

Methods: Polymerease 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 patients with CD.

Results: Significantly more Caucasian patients were DQ2 positive compared to the South Asians (97.2% compared with 83.3%, P=0.002). The haplotype counts (total number of positive chromosomes) for the HLA-A*01, A*03 and DQB1*02 alleles were significantly higher amongst the Caucasians, (P=0.015, 0.015, 0.002 respectively). By contrast, the HLA-A*26, A*32 and Cw*0702 alleles were more frequent amongst the South Asians, (P=0.0001, 0.002, <0.0001 respectively). The haplotype counts for the HLA-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 65.3% of Caucasian compared with 22.2% of South Asian coeliacs (P=0.001).

Conclusions: We have shown preliminary data of distinct HLA associations amongst Caucasian and South Asian patients with CD. This may explain the observed differential presentation in age and symptoms at diagnosis that we have previously reported. It suggests that non-CA regions are likely to be stronger determinants of CD susceptibility in South Asians compared to Caucasians.


331 A COMPARISON OF ANTIBODIES TO TISSUE TRANSGLUTAMINASE WITH CONVENTIONAL SEROLOGICAL TESTS IN THE DIAGNOSIS OF COELIAC DISEASE

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Background: Tissue transglutaminase is now recognised as the autoantigen for antidiomysial antibodies (EMA). Antibodies to tissue transglutaminase (TG1) have been proposed as a valuable test for coeliac disease since they have a sensitivity of 85–100% and specificity of 76–98% which compares favourably with the respective values for EMA (sensitivity 86–100%, specificity 94–100%).

Aim: To evaluate the value of TG1 antibodies for the diagnosis of coeliac disease in our outpatient population.

Methods: Patients presenting with symptoms suggestive of coeliac disease were evaluated using serological testing and duodenal biopsies. Four endoscopic duodenal biopsies were taken and assessed
historically for features of coeliac disease. Coeliac disease was defined as at least severe partial villous atrophy, subtotal or total villous atrophy. The sensitivity, specificity, negative (NPV) and positive predictive value (PPV) of the three serological tests were compared.

**Results:** 78 patients (24 male; mean age 53.0 years) were included in the study, of whom 25 (11 male; mean age 54.4 years) were diagnosed as having coeliac disease. Weight loss (7 v 3; p<0.01) was more frequent in coeliacs compared to controls whereas the frequency of anemia (6 v 10) and diarrhoea (6 v 9) did not differ significantly between the two groups. The sensitivity, specificity, NPV and PPV of IgG (88%; 85%; 94% and 73%) were compared to those for EMA (92%; 98%; 96%; 96%) and antigliadin antibodies (80%; 79%; 89%; 64%) respectively.

**Conclusions:** The diagnostic value of IgG antibodies was intermediate between that of EMA and AGA. Duodenal biopsy remains the gold standard diagnostic test for coeliac disease.

**332 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 12-20% 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.

**333 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 m3 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.

<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>
</thead>
<tbody>
<tr>
<td>Gluten free diet</td>
<td>6</td>
<td>285.8</td>
<td>19.7</td>
</tr>
<tr>
<td>(IQR 2 - 7)</td>
<td>(IQR 151.4-434.2)</td>
<td>(IQR 11.8-36.9)</td>
<td></td>
</tr>
<tr>
<td>Standard diet</td>
<td>1</td>
<td>91.6</td>
<td>20.9</td>
</tr>
<tr>
<td>(IQR 0.5-1.5)</td>
<td>(IQR 71.3-140)</td>
<td>(IQR 7.4-25.8)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Patterns of colonic fermentation improved in all five patients possibly because of reduced malabsorption on a gluten-free diet. Colonic fermentation may be an additional factor producing symptoms in coeliac disease.

**334 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 and immunohistochemistry. In an ex vivo organ culture of treated CD biopsies, the effect of a JAK/STAT1 inhibitor on the glialin-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, glialin induced activation of STAT1 but not SOCS-1. Furthermore, inhibition of STAT1 prevented the glialin-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.

**335 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 toward 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.

<table>
<thead>
<tr>
<th>Villus height (µm)</th>
<th>Caucasians</th>
<th>1st generation immigrants</th>
<th>2nd generation immigrants</th>
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<tbody>
<tr>
<td></td>
<td>353 (48.4)</td>
<td>274 (44.4)**</td>
<td>284 (37.8)**</td>
</tr>
<tr>
<td>Crypt depth (µm)</td>
<td>97 (11.8)</td>
<td>116 (14.9)**</td>
<td>112 (7.7)*</td>
</tr>
<tr>
<td>IEL (per 100um )</td>
<td>7 (1.2)</td>
<td>8 (1.9)*</td>
<td>8.5 (2.9)*</td>
</tr>
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</table>

*p<0.01  **p<0.001

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.

Cell/molecular biology posters

336 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 complementary 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 were tested in 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 the non-HLA linked inherited susceptibility.

337 ROLE OF TRANSCRIPTION FACTOR NF-κB IN CYCLOXGENASE-2 PROMOTER INDUCTION 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 translocation 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 of the human COX-2 gene were constructed into a promoterless luciferase expression vector pGL3. A proximal NF-κB site mutant (–222 to –13) showed a significant increase in luciferase activity compared to the control. A double NF-κB mutant were used. Transfected cells were incubated for 24 hours with live H. pylori (strain 60190, tox++, cagA+). Firefly and renilla luciferase activities were measured.

Mutation of either of 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 increase generation of endothelial cell prostacyclin 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.

Abstract 335

Discussion: Relative villus atrophy and crypt hyperplasia is present in first and second generation immigrants, which may be due to SI inflammation in response to an environmental antigen from their country of origin.
DOWNREGULATION OF \( \alpha/\beta \) 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 colorectal epithelial cells \( \alpha/\beta \) integrin controls glandular differentiation and proliferation. Butyrate stimulates differentiation and induces apoptosis in vitro.

Aim: We investigated whether butyrate induction of apoptosis was associated with perturbation of integrin-mediated cell matrix adhesion.

Methods: Four colorectal cancer cell lines (SW 1222, H729, SW620, LS174T) were studied. Adhesion to extracellular matrix proteins was investigated by a cell-matrix adhesion assay. Expression and cellular localization of \( \alpha/\beta \) integrin were studied in adherent cells after treatment with 4 mmol/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 (\( p=0.003 \)) and type I (\( p=0.01 \)) and IV (\( p=0.03 \)) collagen in LS174T cells. The decreased cell attachment was associated with downregulation of \( \alpha/\beta \) and increase in apoptosis in adherent cells (SW620 9.6±0.5 vs. 3.5±0.2, \( p=0.000 \); H729 6.5±0.4 vs. 2.3±0.1, \( p=0.001 \); LS174T 9.3±0.6 vs. 4.3±0.3, \( p=0.003 \)). No changes in \( \alpha/\beta \), expression and matrix adhesion were seen in non-adherent cells, which were found less sensitive to the butyrate-induction of apoptosis (2.4±0.2 vs. 3.3±0.4, \( p=0.123 \)). Treatment with NS-398 increased apoptosis (5.9±0.08 vs. 2.06±0.14, \( p=0.000 \)) without affecting integrin expression and cellular localization. Downregulation of \( \alpha/\beta \) 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 \( \alpha/\beta \) integrin. Perturbation of cell matrix adhesion may be a novel mechanism by which butyrate induces apoptosis in colorectal cancer cells.

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 poly (HPP) (serrated CRC pathway). In HPP there are multiple, large HPs and an increased risk. If CRC in HPP showed MSI and the MSI-H phenotypic (proximal, multiple, CRCs in females with mucinous, undifferentiated histology and a prominent lymphocyte infiltrate), this would support the serrated CRC pathway.

Aim: To describe the phenotype and microsatellite (MS) status of CRC in HPP to provide evidence for the serrated CRC pathway.

Methods: HPP patients were identified after a national call for cases and using the UK flexible sigmoidoscopy screening trial database. Clinical and histological features were described. Paraffin-embedded tissue samples were microdissected and DNA was extracted. MSI analysis was performed by PCR at Bar25, Bar 26, Mycl1, D25123, APC, D15S221 and D17S250 and compared to genomic or normal tissue DNA. MS status was defined as follows: MSI-H = 3 unstable (\( \geq 1 \) mononucleotide marker); MSI-Low (MSI-L) = 1–2 unstable, MS stable (MS-M) unstable. Tissue samples were analysed by immunohistochemistry for mismatch repair proteins MSH1, hMSH2 and hMSH6.

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 and showed a prominent lymphocyte infiltrate. 6/22 (27%) CRCs were MSI-H and were proximal and showed strong HMLH1 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.

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 colorectal 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 aminostat gastrin (INS-GAS). We have investigated in murine intestinal epithelium in vivo whether alterations in the regulation of apoptosis or mitosis following DNA damage contribute to the procarcinogenic effects of progastrin.

Methods: Apoptosis and mitosis were assessed on a cell positional basis by light microscopic assessment of small intestinal and colonic crypts from 10–12 week mice, following 1 or 8 Gy irradiation. Mice were analysed for gastrin overexpression (hGAS), gastrin overexpression (INS-GAS) and gastrin knockout (GAS-KO) along with their wild-type counterparts (FVB and C57BL/6). Expression was assessed by immunohistochemistry and Western blotting using a rabbit polyclonal primary antibody.

Results: 4.5h following 1Gy and 8Gy irradiation, apoptosis was induced to similar levels in the small intestinal and colonic crypts of all mice. Colonic mitosis was inhibited to almost undetectable levels by 8Gy irradiation in wild-type, GAS-KO and INS-GAS mice. However, significant colonic mitosis persisted in hGAS mice 4.5h following 8Gy irradiation. hGAS mice also showed increased length of colonic crypts compared to FVB and INS-GAS, irradiation caused induction of p21WAF1/CIP1 expression by hGAS and FVB colonic epithelium.

Conclusions: (1) 4.5h after DNA damage by 8Gy irradiation, mice with elevated progastrin exhibit significantly higher levels of colonic mitosis than wild-type or gastrin overexpressing mice. (2) Progastrin induced stimulation of mitosis following DNA damage may account for its procarcinogenic properties.

NSAIDS INHIBIT \( \beta \)-OXIDATION OF PALMITATE AND ARACHIDONATE IN HCT-116 CELLS

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Introduction: Non-steroidal anti-inflammatory drugs (NSAIDS) are useful for prevention of colon cancer. Earlier reports show inhibition of palmitate \( \beta \)-oxidation by NSAIDS and demonstration that elevated cellular arachidonate levels cause apoptosis.

Methods: We hypothesised that inhibition of \( \beta \)-oxidation of arachidonate would lead to arachidonate accumulation and possibly cell death. We determined effects of NSAIDS on palmitate and arachidonate \( \beta \)-oxidation and cell viability. HCT-116 cells were grown to confluence on 24-well cluster plates and were incubated over 2 hours in DBPS with \( ^3 \)H-palmitate or \( ^3 \)H-arachidonate. Effects of NSAIDS on cell death was measured by FACS analysis and confocal microscopy. 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 irradiation. Mice were analysed for gastrin overexpression (hGAS), gastrin overexpression (INS-GAS) and gastrin knockout (GAS-KO) along with their wild-type counterparts (FVB and C57BL/6). Expression was assessed by immunohistochemistry and Western blotting using a rabbit polyclonal primary antibody.

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Conclusions: (1) 4.5h after DNA damage by 8Gy irradiation, mice with elevated progastrin exhibit significantly higher levels of colonic mitosis than wild-type or gastrin overexpressing mice. (2) Progastrin induced stimulation of mitosis following DNA damage may account for its procarcinogenic properties.
A ROLE FOR VON WILLEBRAND FACTOR IN HELICOBACTER PYLORI-INDUCED PLATELET AGGREGATION


Human and animal data have demonstrated platelet aggregates in gastrointestinal vasculature in association with H. pylori infection. We have previously shown that certain strains of H. pylori induce platelet aggregation via the platelet glycoprotein GPIIb. The GPIIb receptor mediates adhesion to von Willebrand factor under high shear. We sought to characterise this interaction and investigate the role of plasma factors such as von Willebrand factor.

An aggregating and non-aggregating strain of H. pylori (60190 and J104) were grown under standard conditions. 50µl of bacterial suspension [4x10⁶ CFU/ml] were added to 50µl of polyclonal anti-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 FACSCaliber flow cytometer. H. pylori strain 60190 bound anti-vWF antibody [mean fluorescent intensity: polyclonal anti-vWF 324±75 and 112±4 for control; monoclonal anti-vWF 52±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 223±23, p=0.005, n=3, test]. In addition, H. pylori 60190 failed to induce aggregation of washed platelets [5.5±3.9% aggregation, n=3]. However, H. pylori pre-incubated in platelet poor plasma induced platelet aggregation [28±6.4% aggregation, n=3]. The polyclonal anti-vWF antibody inhibited this platelet aggregation (95±3.9% 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 GPIIb. 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 survive in culture are unclear, but the single most important factor is that cells die from detachment-induced cell death (DICD) when stripped from the underlying lamina propria. Understanding the mechanisms that result in this form of apoptosis may provide insights into the long-term primary culture of human enterocytes.

Methods: Human duodenal biopsies were isolated from consenting patients presenting with irritable bowel syndrome and iron deficient anaemia. All biopsies showed normal histology. Whole biopsies were incubated for 4 hours at 4°C in cell dissociation fluid (Hirsperson), after which time they were shaken vigorously to free the enterocytes from the lamina propria. Both the enterocyte fraction and the lamina propria were washed and assessed for purity using Western blotting. Fractions were incubated at 37°C in serum free media for various times. Apoptosis was assessed by assaying surface expression of phosphatidylserine (PS) using flow cytometry and by DNA laddering. 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: Matrisperse treatment of human duodenal biopsies produces a pure, non-apoptotic population of enterocytes. Isolated enterocytes undergo rapid DICD as assessed by surface expression of PS and DNA laddering. DICD is independent of de-novo protein synthesis, is evident within 30 mins of detachment and is accompanied by the activation of caspase 3, caspase 8 and caspase 9. In support of these observations cleavage products of the genomic surveillance protein PARP and the caspase 8 substrate BID were detected. DICD can be delayed but not halted by the addition of the broad spectrum caspase inhibitor (Boc-D-FMK) and the selective caspase 8 inhibitor (Z-IETD-FMK).

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. Alginic biopolymers are widely used in the treatment of gastroesophageal reflux disease (GORD) and impact cytoprotective biological effects. In this study we have investigated the impact on fluid phase endocytosis (FPE) of alginites and EGF.

We have used four oesophageal cell lines: 3H-palmitate, 3H-arachidonate viability assay, and FPE. EGF and alginate added together upregulate FPE. Alginate and EGF antagonists and proton pump inhibitors (PPI).

Results: 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, of which some 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 alginate biopolymers and how these properties impact on FPE. This in turn may lead to improvements in medications aimed at the treatment of oesophageal disease.

347 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 metalloproteinase (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 receptor mediated endocytosis.

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 (1μM) and or the addition of 3 different CCK-2 receptor antagonists (YM022, JB95008 and JB95135) and INW1153 and JMV1155. The cell lines investigated were: NIH 3T3 fibroblasts, NIH 3T3 transfected with classical CCK-2 and truncated CCK-2 receptors, and Matrigel invasion chambers were used to assess the invasiveness of the cells with GlyG17 and or CCK-2 stimulation.

Results: In human fibroblast cell lines transfected with MT1-MMP produced a significant increase in pro and active MMP-2 (p<0.05) and proMMP-9 (p<0.03) at the protein level, following stimulation by GlyG17. Only the truncated CCK-2 receptor NIH 3T3 transfectedants had a significant increase (p<0.05) in proMMP-2. None of the cell lines tested had a significant change in gene expression for the MMPs tested. JB95008 was the only CCK-2 receptor antagonist that significantly reduced GlyG17 increased MMP-2 expression (p<0.03). With the stimulation of GlyG17, only the HT1080 MT1-MMP transfectants had a significant (p<0.05) increase in their matrigel invasion.

Conclusion: The stimulation of cells by GlyG17 has been shown to be cell line specific but not receptor specific. GlyG17 has the ability to increase protein levels of pro and active MMP-2 and proMMP-9. GlyG17 increases the invasiveness of cells that already express active MMP-2 but has no effect on cells that express only the pro form. The blocking of the CCK-2 receptor reduces GlyG17 stimulation of MMP-2 expression.

348 A STUDY INTO THE RELATIONSHIP BETWEEN EPIDERMAL GROWTH FACTOR, ITS RECEPTOR AND GANGLIOSIDES GM1 AND GM3
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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 GM1 and GM3 by electron microscopy.

Methods: Tissue samples from human normal fibrosarcoma HT1080 transfected with MT1-MMP, and the mouse fibroblast NIH 3T3 transfected with classical CCK-2 or truncated CCK-2 receptors. Gangliosides on RME.

Results: EGF is a 65 kDa polypeptide that has a role in tissue repair, cell proliferation, ulcer healing and cell migration. Many gangliosides have been identified on the basis of their carbohydrate structure that is mainly expressed on the outer surface of the plasma membrane. Gangliosides act like receptors for some viruses, bacteria and bacterial toxins allowing passage into the cell.

Conclusion: The EGFr and GM1 and GM3 by electron microscopy. 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. Gm2 inhibits the mode of action of EGFr in squamous 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 EGF binds to EGFr, and that Gm2 acts as a monitor for the binding of EGF to EGFr.

349 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 metastatic change to Barrett’s epithelium, a precursor of oesophageal adenocarcinoma. Previous studies in animal models and human epithelial cells suggest that stress activates 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 glycophane 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 metastasis-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 tissue 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 lysates 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 ura lysates demonstrated a reversion of SEP70 immunoreactivity to different molecular weights.

Conclusion: The laddering of SEP70 immunoreactivity may be due to detection of sub-cytoplasmic 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.

350 SODIUM BUTYRATE DOWNREGULATES IGF-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 amplicons, IGFBP3 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 IGFBP-3 was dependent on de novo protein synthesis, Caco-2 cells were stimulated with butyrate in the presence and absence of cycloheximide (CHX). At doses of up to 10μM, CHX did not affect the butyrate-induced down-regulation of IGFBP-3. Butyrate caused an up-regulation of IGFBP-2 mRNA and this effect was again not altered by the protein synthesis-blocking effects of CHX. We verified that 10μM CHX inhibited protein synthesis by interrupting IGFBP-2 expression.

Conclusion: Our data indicate that the modulatory effects of butyrate on IGFBP-2 and -3 are independent of de novo protein synthesis. Therefore, butyrate’s effects are not through the synthesis of a repressor of IGFBP-3. This suggests that butyrate has direct inhibitory effects which may involve the modification of the acetylation status of proteins in the nucleus.

ENDOSCOPY POSTERS
352–391

352 AUDIT: TO DETERMINE THE QUALITY OF INFORMED CONSENT IN PATIENTS ATTENDING FOR OGD, COLOSCOPY AND FLEXIBLE SIGMOIDOSCOPY
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An audit carried out last year examining the degree of informed consent in competent adults found that although the majority of patients understood what the procedure involved and had been interviewed by a health care professional, 34% had poor understanding of the benefits of the test and 75% had little or no idea of any associated risks. This audit determines whether modifications made to information to include risk sent to patients in the light of these findings led to an improvement in the level of understanding.

118 patients were interviewed. As last year, 97% were aware which investigation was to be performed and the region to be examined. 69% (63% last year) had received information prior to the procedure, with 80% acknowledging receipt of printed information. 99% of patients had spoken to a health care professional, a proportion similar to last year. Only 60% (88% last year) were deemed to have a good understanding of what was to occur during the test and 66% (90% last year) were aware of what was to happen after the procedure. 70% (34% last year) had poor understanding of the benefits of the test. 48% (25% last year) were aware of the risks.

Conclusion: Changing the literature produced an improvement in understanding of associated risks, however, only 30% of patients were aware of the benefits of the test, and less than half were clear on what would happen during and after the investigation. This may reflect inter-observer variation, although the question does arise whether a certain proportion of patients have the cognitive ability to grasp the information presented to them—it may be pertinent to explore this issue further. Asking patients to complete a checklist is one way of ensuring that they have read material sent to them and been given the opportunity to ask questions.


Abstract 353

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Referred by TDR</th>
<th>Open access referral</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic oesophagitis</td>
<td>14%</td>
<td>10%</td>
<td>0.2</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>12%</td>
<td>7%</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastric/dud. erosions</td>
<td>6%</td>
<td>8%</td>
<td>0.3</td>
</tr>
<tr>
<td>Oes/gastric cancer</td>
<td>6%</td>
<td>1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
<td>10%</td>
<td>0.3</td>
</tr>
<tr>
<td>Normal findings</td>
<td>51%</td>
<td>64%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusions: Significantly more upper GI cancers and serious benign diseases can be found within a short period to comply with the TDR scheme. However, some GPs appear to over read alarm symptoms, and this may lead to some inappropriate referrals. Better awareness of appropriate urgent referral criteria is needed in order to ensure that the best possible use is made of the resources available for this initiative.
THE DEVELOPMENT OF A PSYCHOMETRIC SCALE TO PREDICT THE INFLUENCE OF MEDICAL AND NON-MEDICAL FACTORS UPON GENERAL PRACTITIONERS’ DECISIONS TO REFER PATIENTS WITH GASTROINTESTINAL (GI) SYMPTOMS

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Background: Factors that influence GPs’ referral decisions for GI complaints have received little attention in the literature. A greater understanding of this process is essential for developing guidelines and improving services, yet retaining aspects of the valuable primary care screening function. This has become 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, 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 malignancy. 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 benign explanation for presenting symptoms.

Conclusions: The scale was well received as a simple and quick method for assessing the relative importance of factors that influence GP referral decisions. This tool is helping us to work with primary care colleagues to develop our direct access booking system.

ULCER HAEMOSTASIS BY THE HEATER PROBE: BIGGER MAY NOT BE BETTER

1Western General Hospital, Edinburgh, UK; 2Aberdeen Royal Infirmary, Aberdeen, UK; 3Nineillews Hospital, Dundee, UK; 4Gartnavel General Hospital, Glasgow, UK; 5Scottish National Blood Transfusion Service, UK; 6University of Edinburgh Medical School, Edinburgh, UK.

Introduction: The heater probe is a widely used thermal modality, which is used in many centres to effect ulcer haemostasis. It has been stated that the large (3.2 mm) probe is more effective than the small (2.4 mm) probe, but this statement is not supported by 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 (1200 and 1600 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.

Conclusions: The efficacy and safety of both heater probes, used in association with endoscopic injection is similar.

VARIATION IN REPORTING OF GASTROSCOPY BY DIFFERENT ENDOSCOPISTS AT A SINGLE CENTRE

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Introduction: Gastroscopy is a fundamental investigation for the gastrointestinal endoscopist. 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.

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Conclusions: The efficacy and safety of both heater probes, used in association with endoscopic injection is similar.

Abstract 355

Endoscopic diagnosis Total Range (%) P value

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>880</td>
<td>18–60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastritis</td>
<td>323</td>
<td>4–65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>263</td>
<td>2–33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>310</td>
<td>2–22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>440</td>
<td>8–36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>450</td>
<td>18–35</td>
<td>&lt;0.004</td>
</tr>
</tbody>
</table>

Conclusions: There are major discrepancies in the reporting of endoscopic examinations. We may be failing to accurately and consistently report our findings. This has major implications for the patients’ perception of their illness, the GPs’ ongoing management and consequently the nation’s health costs.

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

COLONOSCOPIC SKILL: THE LEARNING CURVE REVISITED

Royal Cornwall Hospital, Torbay Hospital and Bristol Royal Infirmary, UK.

Although there has been substantial progress in the ability of trainees 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 competence 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 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 appropriate scores that are summated 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 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 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 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 when there is sustained achievement of the required standard.
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

K. Burn1, R. Bicker2, G.D. Bell3, S. Dogramadzi1, C. Allen1. 1School of Computing, Engineering and Technology, University of Sunderland, UK; 2Mechanical, Materials and Manufacturing Engineering, Newcastle University, UK; 3Medical Sciences Faculty, Sunderland University, UK.

Introduction: There is increasing interest in the use of both variable stiffness colonoscopes and thinner “floppier” 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 unique, computer based system has been developed that enables EI to be continuously measured along the entire shaft of an endoscope in c60 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: The new system accurately logged EI data in a fraction of the time (<60 seconds) that it had previously taken using our manual system. It recorded data at 1 mm (compared to 100mm) intervals and had the additional advantage over the manual system that the EI data could be saved to computer in raw and processed forms. These could then be displayed in either numeric or graphical format using standard Windows applications such as Microsoft Excel. A systematic comparison of the EI of a number of commercially available endoscopes is now in progress.

A CASE CONTROL STUDY OF NITROUS OXIDE/OXYGEN (N2O/O2) AND BENZODIAZEPINE/OPIATE IN LOWER GI ENDOSCOPY


Intravenous benzodiazepine/opiate (IV) is normally used for sedation and analgesia in lower GI endoscopy. Disadvantages of this approach include significant cardiopulmonary complications and prolonged recovery time. The aim was to compare N2O/O2 (Gas) with IV. A prospective, randomised controlled trial was performed by the nurse endoscopist in 21 (14%) cases with no complications.

Results: 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.

Conclusion: A nurse endoscopist with an experienced background in flexible sigmoidoscopy can, with specialised training, safely perform to progress colonoscopy for diagnostic referrals.

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


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 localise 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 not of surgical or 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.

364 COMPARISON OF THE DIGITAL ACQUISITION SYSTEM AND SCREEN FILM SYSTEM DURING ERCP

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ERCPs are employed in the diagnosis and treatment of biliary and pancreatic disorders. Modern fluoroscopy systems usually allow acquisition of images for hard copy using a digital acquisition system (DAS) instead of a screen-film system (SFS). It is thought that the DAS is associated with a lower radiation dose.

The aim of the study was to prospectively compare the radiation doses to patients from digital imaging and the screen-film system. DAP reading [Gy.cm2] which is a convenient measure of radiation exposure, screening time, and number of films were recorded.

Data was recorded on 33 patients (10 diagnostic) using the digital imaging and 20 (8 diagnostic) using the screen-film system. Average DAP for the DAS was 16.8 Gy.cm2 for diagnostic and, and 63 Gy.cm2 for therapeutic ERCP. Average DAP for the SFS was 15.3 Gy.cm2 for diagnostic, and 66.6 Gy.cm2 for therapeutic ERCPs. 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 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 to assess the relationship between the urgency of the endoscopy, as designated by the gastroenterologist, and the waiting time.

The aim of the present study was to determine the relationship of the urgency of the procedure to 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 alongside 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 134 days, 59 days, and 19 days respectively. The proportions of cases in each category and the 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 92% of urgent cases. Significant lower GI pathology was found in 38% 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.
ACHIEVING THE “TWO WEEK STANDARD” FOR SUSPECTED UPPER GI CANCERS: CONTINUING PAIN WITH MINIMAL GAIN: A RETROSPECTIVE AUDIT

Introduction: Gastrointestinal endoscopy units UK wide continue to strive to meet the two week standard for diagnosis of suspected upper GI cancers. In many cases this has put additional strain on already overstretched departments with negligible improvement in outcome and potential counterproductivity.

Methods: We performed a retrospective audit of patients referred for urgent open access gastroscopy over a six month period. Referrals were made on a standard proforma or letter marked “urgent” and mentioning the word “cancer”. These were coordinated via our Cancer Office with fax and online facilities. We collected clinical and demographic data and analysed both the decision to refer to actual referral time (ideally 24 hours) and the receipt of referral to appointment time.

Results: Data were collected on 79 patients (46 female and 33 male), mean age 69 yrs, from April-September 2001. All but three were faxed proforma referrals. One patient DNA’d, 33% had a normal endoscopy. Only three cancers were detected [4%], all within 14 days of referral. These were all unresectable OG junctional adenocarcinomas.

Conclusion: Whilst the majority of patients were gastroscoped within two weeks of referral, a significant number fell short of the standard. This was due to in part to a delay in GP referral time. Despite this, it remains to be seen whether overall achievement of the two week standard translates into reduced mortality from upper GI cancer.

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TABLE 1: PATIENT CHARACTERISTICS AND GENERAL PRACTITIONERS’ REFERRAL DECISIONS FOR GASTROENTEROLOGY

<table>
<thead>
<tr>
<th>Abstract 366</th>
<th>GP referral time</th>
<th>Within 24 hrs</th>
<th>24–48hrs</th>
<th>&gt; 48hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral-scope time</td>
<td>Within 2 weeks</td>
<td>51/79 (65%)</td>
<td>12/79 (15%)</td>
<td>16/79 (20%)</td>
</tr>
<tr>
<td></td>
<td>2–3 weeks</td>
<td>59/79 (75%)</td>
<td>14/79 (17%)</td>
<td>5/79 (8%)</td>
</tr>
</tbody>
</table>

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367 VOLUME AND DISTRIBUTION OF GP REFERRALS TO A GASTROENTEROLOGY (GI) UNIT: PLANNING FOR A POOLED, WEB-BASED, DIRECT BOOKING SERVICE
A. Douglass, P.A. Cann. Endoscopy Centre, James Cook University Hospital, Middlesbrough, UK

Introduction: A pooled Medical/Surgical approach to GI services would enable referrals to be distributed according to Consultant specialist interest, allow an even spread of workload, avoid problems arising from leave, give direction to clinic, or procedure as first contact and facilitate efficient prioritisation. Do we know how much we all get of what?

Aims & Objectives: To examine the volume, distribution, and subgroup clusters of GI referrals from GPs to a busy GI unit. To explore options for redistribution/prioritisation of these referrals.

Methods: The unit serves a 300 000 population and provides open access (OA) gastroscopy and colonoscopy services. It employs three GI physicians, three colorectal surgeons, and one upper GI surgeon. All GI (Medical, Surgical, and Open Access) referrals from GPs to our unit for a two month period were reviewed and analysed. General Surgical (non GI) referrals excluded. Main classes: dyspepsia, upper GI (i.e. dyspepsia, GORD, or upper abdominal pain), and lower GI (i.e. isolated rectal bleeding, change in bowel habit +/- rectal bleeding (Ch.BH +/- RB)).

Results: Expressed as total number for main classes per sub-service and (% over 45 years of age). 1303 referrals were received in the two months, further examples, there were 12 patients with unexplained iron deficiency anaemia without any GI symptoms. 111 referrals were labelled urgent and 26 as “Two week rule” referrals.

Discussion: This and the more detailed analysis of our total GI referral load from primary care, is allowing us to engineer a restructuring of the number of “slots” we must make available on the “pooled effort direct booking system” for each clinical sub-group category. It also informs our designation of “appropriateness” of these slots for relevant clinician, nature of first contact, and speed of first contact.

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TABLE 2: 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. 31 = normal villi; 22 = stunted villi; 3 = “ridges and pits”; 4 = flat. For this, 17 consecutive patients with known CD were studied over an eight month period. Z score was determined by the endoscopist. The pathology analysed 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 Z1 (mean 2.3). Seven cases were in group C, two were Z3 and five Z4 (mean 3.7). The sensitivity of “Zoom” endoscopy in identifying villous atrophy is 100%. Authors: 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
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PEJ insertion was attempted in 17 patients (10M, 7F, median 74 years) with an indication for enteral feeding. Four were unable to tolerate standard percutaneous endoscopic gastrostomy (PEG) feeding due to intractable vomiting or feed regurgitation and 13 were not suitable for standard PEG insertion. Of these, three had abnormal gastric anatomy preventing PEG insertion, four had previous gastric surgery, three had diabetic gastropathy, one had oesophageal-gastric cancer, one had intractable vomiting with nasogastric feeding, and one had meconium ileus equivalent due to cystic fibrosis requiring N-acetyl cysteine perfusion. Patents were sedated with midazolam (mean 4.9mg) with the addition of pethidine (mean 50mg) in six patients and hyoscine (mean 28mg) in five patients. Propylthiouracil (mean 180mg) was used in eight patients and other combinations of antibiotics in eight. A videocentroscope 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 a carefully atraumatic transition into the abdominal wall and the jejunum punctured with the trochar from a standard 16 French Gower Merck Corflo PEG kit. The guide wire passed through the trochar was retrieved with biopsy forceps and the endoscope inserted. The feeding tube was then connected and pulled through the abdominal wall into position. If transillumination was not achieved within 30 minutes the procedure was abandoned. The procedure was successful in 13 of the 17 patients (76%). The four failures were due to inability to transilluminate. Two of these had standard PEG insertion, one with a jejunal extension, and one had a surgical jejunostomy. One patient with advanced oesophagogastric cancer died three days post procedure from aspiration pneumonia. One patients developed refeeding syndrome from which they recovered. Seven patients died from their underlying disease or complications. Of the seven deaths, three died from sepsis, one from respiratory failure, one from perforated diverticulitis, and one from aortic dissection. Two patients underwent laparotomy for peritonitis, one due to perforated diverticulitis and the other due to perforated gastric ulcer. The overall caecal intubation rate was 93% (72–100%).

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.

Method: Details of referral, examination, endoscopist, complications, and follow up were recorded prospectively. Patients completed 100 point visual analogue scales for pain and satisfaction following their procedure.

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 10 weeks (0–56) for routine cases. The overall caecal intubation rate was 93% (72–100%).

372 THE IN VITRO ASSESSMENT OF A NOVEL “CONTINENT” AND DISPOSABLE CORRUGATED SIGMOID STIFFENING OUTFLOW OVERTURE FOR COLONOSCOPY
G.D. Bell, J. Buller, S. Dogramaci, J. Hancock, D. Nylander, J. Painter, K. Burn, R. Bicker, K. Burn. Medical Sciences Faculty, Sunderland University, UK; Advanced Surgical Concepts, Bray, Eire; Department of Electrical and Electronic Engineering, Newcastle University, Newcastle, UK; Department of Medicine, Sunderland Royal Hospital, UK; School of Computing, Engineering and Technology, University of Sunderland, UK; Department of Mechanical, Materials and Manufacturing Engineering, Newcastle University, UK

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 2000;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 faecal 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 flappiest mode. Magnetic endoscopy 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 experienced endoscopists. The valve at its tip remained airtight despite numerous passages of the endoscope along the ASCOT simulator. The ASCOT was less stiff (p<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.

373 ST.THOMAS’S HOSPITAL BARRETT’S OESOPHAGUS AUDIT
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Introduction: Barrett’s oesophagus was first described in 1950 and is said to have an increased cancer risk of between 20 and 125 fold. This has led to endoscopic surveillance programmes.

Aims: To assess the number of patients with Barrett’s oesophagus found on endoscopy between November 1999 and December 2000, histological characteristics and whether follow up had found any carcinomas during that period.

Methodology: Data were collected from the endoscribe reporting system using the terms “Barrett’s” and “oesophagus”. Histology was found via the RRS computer reporting system and analysed in relation to the OGD reports.

Results: 250 patients were found (181 female, 99 male) to have an endoscopic diagnosis of Barrett’s out of a total of approximately
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 UTILITIY OF TERMINAL ILEAL (TI) BIOPSIES AT ROUTINE COLONOSCOPY

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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 calendar year which reported taking TI BXs. Only colonoscopies performed by Consultant Gastroenterologists and Specialist Gastroenterology Registrars were used. The Endoscribe programme, set up in the endoscopy suite of our 630 bed Dublin teaching Hospital, was the means by which we accessed the reports. We then cross referenced each individual TI BX taken at colonoscopy with its histopathology report.

Results: Our study period was 2 Oct 2000—2 Oct 2001. A total of 111 TI BXs were sent for histology, with 106 being actual TI histologically and thus five proved to be colonic mucosa. These results showed a mismatch rate of 4.5% between endoscopic TI and histological TI. We also examined the indications for procedure, these included: altered bowel habit, unexplained abdominal pain, weight loss, blood per rectum, anaemia (iron and B12), polyp/carcinoma surveillance, 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

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Background: Colonoscopy is the investigation of choice for examining the colon but as the demand for colonoscopy increases and JAG begin to specify quality targets, there have been shortfalls in practise confirmed by a recent national audit. We have developed the role of nurse colonoscopist and now present a prospective comparison of doctor and nurse performed colonoscopy.

Methods: Patients attending for routine diagnostic colonoscopy were invited to participate. Taking TI BXs. BXs were performed using standard videendoscopes and were video recorded for independent review. Endoscopists were instructed to use midazolam, pethidine, and buscopan according to their usual practice. Endoscopists and nurse assistants graded the patients’ pain and tolerance on visual analogue scales (VAS) and a validated questionnaire and VAS were given to the patient following the procedure.

Results: 84 patients (38 female, aged 29 to 83 years) were examined by the doctor and 83 (48 female, aged 23 to 87 years) by the nurse. Intention to treat caecal/ileal intubation rates were 98/83 % and 94/72 % respectively. Failure to reach the caecum was due to obstructing cancer (1) and diverticular disease (1) in the doctor group, and patient discomfort (3), poor preparation (1), and obstructing Crohn’s disease in the nurse group. Pain and tolerance scores were similar but the nurse used more midazolam and pethidine. The pathological spectrum was also similar but with more diverticular disease in the doctor examined group. No significant complications occurred.

Conclusions: Appropriately trained nurses perform safe and effective colonoscopy examinations with caecal and ileal intubation rates exceeding JAG recommendations. Expansion of the nurse colonoscopist role may help to meet the increasing demand for diagnostic colonoscopy.

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

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Background: Self expanding metal stems 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 stent 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 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 scope” technique and a large channel (4.2mm) operating gastro-scope (Olympus GIF 27240). Pre-dilatation of the stricture was not performed routinely.

Results: 15 patients, median age 78 years, (range 60–92 years) had a total of 15 enteral stents. Outflow obstruction was due to carcinoma of antrum (n=3), pyloric canal (n=3), duodenum (n=1), bile duct (n=3), and pancreas (n=5). One patient had three stents placed in series to “bridge” a long stricture involving the gastric antrum and duodenal cap. One patient required a second stent four days later, due to proximal stent migration. One patient with a pyloric canal tumour was found to have a second distal duodenal stricture after
Abstract 378  The surface roughness of 4 biliary stents. Ra value is the average of 3 measurements from 10µm² AFM images; standard deviation of the data is shown in the brackets.

<table>
<thead>
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<th>Material</th>
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<th>Design</th>
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<td>Olympus</td>
<td>Tannenbaum-type Doublelayer, Tannenbaum type</td>
<td>13.26 (2.09)</td>
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<td>Polyethylene</td>
<td>Boston Scientific</td>
<td>Rapid Exchange</td>
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Conclusion: AFM images the native stent surface within air or liquid with a higher resolution and allows quantification of surface roughness. AFM is a useful tool for the study of stent materials and proposed surface chemistry modifications prior to clinical trials.

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

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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 (UGC) 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 (OAEA) 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 “Endoscribe” for OAE and prospectively for RAUGICS. Two six month periods were compared (OAEB: 01.01.00 to 30.06.00; OAEA & RAUGICS: 01.01.01 to 30.06.01). Major diagnoses and disease stage of cancers were verified by case record review.

Results: After launch of RAUGICS: (a) total DRs increased by 33% (953 to 1264) with 51% of DRs (645/1264) designated as requiring the “fast track” service [rapid endoscopy, then clinic review]; (b) the prevalence of UGI cancer amongst DRs overall was unchanged (1.57% v 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 (OAEB versus RAUGICS).

Conclusions: Referral criteria were effective in channelling patients with UGI cancer into the RAUGICS arm of the direct access service, but demand for “rapid access” was high (half of all DRs). The low cancer rate [3.1%] suggests either poor specificity of referral criteria or a high level of “inappropriate” referrals.
**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 three changes 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 a description of the proposed system 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 considered gastroscopy was 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 inpatients with GI bleeding and anaemia although more selective referral questions may improve the appropriateness of referrals. Pre-procedure consultation is more appropriate for most other categories of inpatient referrals.

**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 incorporated as algorithms within the software of the computerised decision support booking system. This will enable the most appropriate slot for the patient to be identified and booked directly in real time. “ Appropriateness” will relate to relevant clinician, nature [clinic or procedure] and speed of first contact and provide patients with some choice of appointments.

**Aims & Objectives:** To assess GPs’ attitudes to the principles, design, and their eventual usage of such a system.

**Methods:** 21 GPs were given a description of the proposed system and asked to rate each of eight potential benefits on a 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 provided 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 systems (mean 4.37). 52% of GPs indicated that they would use the system in real time only if it generated no more than two additional minutes on consultation times. 21% of GPs were concerned that the system could increase administrative workload, and create unrealistic expectations of open access services for patients.

**Conclusions:** The majority of GPs recognised potential benefits of the proposed system, but the impact on consultation times is a core design issue that will determine acceptance and usage of such a system. Other members of the primary care team may help to minimise the need for the GP to spend “real time” online.

**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 HAEMORRHAGE**

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**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 57%, varices...
15%, normal 12%, erosions 9%, oesophagitis 9%, Mallory-Weiss tear 2%, other 16%. Endoscopic therapy was required in 29 cases (30%). The overall Mortality Rate was 10.5%.

Conclusion: The proportion of patients in this series endedoscopy within 24 hours (92%) compares favourably with published data (50 and 56% in the BSG National Audits)1 1. 17/93 patients underwent out of hours endoscopy including seven with variceal bleeding. The appropriate provision of a 24-hour bleeding service is possible in a small unit with the collaboration of medical and surgical Endoscopists.


Self-administered phosphate enema in bowel preparation for flexible sigmoidoscopy: an audit of efficacy and patient satisfaction

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Background: Patients attending endoscopy for a flexible sigmoidoscopy (FS) examination were being prepared using picolax except one doctor who used phosphate enemas on arrival. Recent research by W. Akin et al (2000)1 has shown that an phosphate enema administered on the day of the examination is as effective as picolax. To see if this could be successful in our endoscopy unit an audit was conducted.

Aims: To improve the way in which patients are prepared for (FS) without compromising the quality of bowel preparation.

Methods: 53 Patients were selected using two (FS) lists and had the option of taking the enema at home instead of picolax for bowel preparation. A questionnaire was prepared for patients to complete while they were waiting for the (FS). A note was made of patients unable/unwilling to administer the enema. Nursing and medical information was collected to assess the acceptability and quality of bowel preparation.

Results: 98% of patients administered the enema successfully at home. 74% of the (FS) tests were completed to 60cm. 100% of patients using the enema would use it again, 12% telephoned the department for advice, 38% experienced mild side effects, and 27% needed help from someone at home. The bowel preparation was excellent to good in 75% of cases.

Conclusion: Patients found the enema easy to use and acceptable as a method of bowel preparation. Although only a small number of cases were audited the results are very similar to those reported in the BMJ 1. Akin et al: BMJ 2000;320:1504–9

Use of a pair of pressure sensitive gloves to determine mechanical work done during either OGD or colonoscopy: a pilot study in 10 patients

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Introduction and aims: Torque steering is now the preferred method of teaching intubation of the tortuous sigmoid colon. One of the criticisms of many teaching simulators is that the “feedback” forces are not 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 workers1. 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 containing 20 calibrated piezo electric 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.


Are multiple biopsies necessary if a colonoscopy is normal?

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Aims: To correlate the histological and clinical findings in patients with a macroscopically normal, total colonoscopy.

Method: A search was made of all colonoscopy reports performed during 2000. Reports from patients with a macroscopically normal, total colonoscopy in which a set of serial biopsies (caecum, ascending, transverse, descending, and sigmoid colon and rectum) were represented both graphically and numerically using specially written software.

Results: See table.

Conclusions: Five cases of IBD (inflammatory bowel disease/microscopic colitis) were identified in 282 patients. In all diarrhoea was a presenting symptom (i.e. 4% of patients with diarrhoea had IBD). If diarrhoea was not an indication no patients were found to have IBD on serial biopsies. We recommend serial biopsies should be taken in patients with a normal colonoscopy but only if the predominant symptom is diarrhoea.
AN AUDIT OF ROUTINE ILEOSCOPY: PROCEDURE TIME AND DIAGNOSTIC YIELD
S. Cherian, A. Cherukuri, P. Singh. Staffordshire General Hospital, Stafford ST16 3SA, UK

Introduction: Ileoscopy is not routinely attempted because of its perceived technical difficulty. We believe routine ileoscopy is useful in quality assurance and 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 414 had biopsies. Ileal Crohn’s was identified in 11, non-specific ileitis was 19, nine additional positive histologies were as follows: ileal Crohn’s, one GAVE: eventually required Argon plasma coagulation and six oesophageal carcinomas, 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 44–98). 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.

Conclusions: Laser therapy is safe and an effective method of palliation for inoperable malignant ileal obstruction when performed in a District General Hospital setting by an experienced endoscopist.

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), 5 (16%) chronic obstructive airway disease (COAD), and three (9%) had other. Median number of procedures was 4 ± 1.2 over a duration of 4 ± 1.9 months. Nine (29%) remained alive (one colonic angiodysplasia, three tubulovillous adenoma, two rectal carcinoma (later had surgery), one sigmoid adenoma and one recto-sigmoid carcinoma). Complication rate was 0%.

For the 64 upper gastrointestinal laser procedures, 39 (61%) had oesophageal carcinoma, 15 (23%) gastric carcinoma, six (8%) stent overgrowth, one (2%) oesophago-gastric carcinoma, one (2%) gastric arteriovenous ectasia (GAVE), one (2%) Hereditary haemorrhagic telangiectasia (HHT), and one (2%) gastric angiodysplasia. 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.

Conclusions: 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.

ABDOMINAL PAIN FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY
A. D. Gilliam, N. Davidson, K. Mylankol, D. Ziegler, E. P. Perry, J. D. Harrison. Department of Surgery, Scarborough Hospital, Woodlands Drive, Scarborough, YO12 6QJ, UK

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.
CURRENT MANAGEMENT OF IRON DEFICIENCY ANAEMIA BY GENERAL PHYSICIANS DOES NOT COMPLY WITH BRITISH SOCIETY OF GASTROENTEROLOGY GUIDELINES

H.R. Ferguson, P. Murphy. Department of Gastroenterology, Craigavon Area Hospital, Northern Ireland, UK

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 antenomalous colonic or rectal anomalies 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 G1 tract investigation although five patients were diagnosed with carcinoma. No cases of coeliac disease were detected, but only 18% had antenomalous 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.

SPEED OF DIAGNOSIS OF UPPER GASTROINTESTINAL CANCER: DOES THE METHOD OF REFERRAL MATTER?

J.G. Williams, S. Gheorghiu, W.Y. Cheung. Swansea Clinical School, University of Wales, Swansea SA2 8PP, UK

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 loss and isolated dysphagia occurred in 14 patients (youngest 52 years) and isolated abdominal pain or dyspepsia was noted in eight (youngest 63 years).

We conclude that if upper GI cancer is suspected patients should be referred for “one-stop” assessment, or admission, rather than outpatients. Cancer may present as isolated abdominal pain or dyspepsia.

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 (T/L) 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. Nonuniform 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.

P53 MUTATION DOES NOT INFLUENCE COX-2 IMMUNOREACTIVITY IN GASTRIC CARCINOMA

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Both COX 2 over-expression and p53 mutation are common findings in gastric adenocarcinoma, being seen in 60% and 40% of cancers respectively. Recently, it has been suggested that wild type p53 expression suppresses COX-2 mRNA transcription by competing for the COX-2 promoter site. If this is the case, COX-2 expression should be markedly increased in tumours with mutated p53 compared with those with wild type p53.
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 osteoskeletal 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.

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Abstract 395

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

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Background: Regional lymph node metastasis in colorectal resections is routinely detected by examination of H&E stained tissue sections. There is no consensus regarding the clinical significance of lymph node micrometastasis detected solely by immunohistochemistry.

Design: Formalin fixed, paraffin embedded tissue sections of all pericolic lymph nodes dissected from 155 patients with Duke’s A/B colorectal cancer who had undergone a curative resection were immunostained using cytokeratin antibodies (Pan cytokeratin and AE1/AE3). Pre-operative and follow up information was sought by review of case notes and death registration where appropriate. Study end points (adverse outcome) were tumour recurrence and cancer related death. Five patients who died in the immediate post-operative period and 41 patients who received pre/post-operative radio/chemotherapy were excluded from adverse outcome analysis.

Results: Eight hundred and ninety eight lymph nodes (range 1–20, median 5) were identified in the 155 resection specimens. Immunohistochemically detected micrometastasis, generally as single cells in the subcapsular sinus, was present in 155 (17.3%) lymph nodes (range 1 to 10, median 2) from 67 (43.2%) of patients (7/24 Duke’s A, 58/115 Duke’s B, 2/16 Duke’s A/B with history of pre-operative radiotherapy).

Adverse outcome was recorded as 15% of 52 patients with micrometastasis detected by immunohistochemistry in comparison with 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.

Abstract 396

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

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Introduction: The two week wait scheme for patients with suspected cancer was introduced in April 2000. Guidelines as to which patients are suitable for this scheme have been produced. The evidence base that the scheme will produce clinical benefit is limited.

Methods: All patients referred to the two week cancer wait scheme in its first year with suspected gastro-oesophageal cancer (GOC) or colorectal cancer (CRC) were audited. After taking the history and examining the patient, the consulting doctor was asked to assess the indication for referral. The eventual diagnosis was recorded and correlated to the indication for referral. The out-patient (OP) waiting times for non-urgent cases during the year were documented.

Results: 394 patients were referred with suspected CRC and 280 with suspected GOC. The table shows the commonest referral indication, defined by the guidelines, and the pick up rate for cancer. 27% of GOC and 46% of CRC were detected in patients referred via the scheme. The OP waiting times for non-urgent cases increased from 9 to 16 weeks during the year.

Discussion: The guidelines are inadequate for detecting patients with cancer and are not adhered to for many referrals. The majority of cancers do not present through the scheme. It is likely that the scheme is having an adverse effect on non-urgent waiting times.
A SEVEN YEAR EXPERIENCE OF MANAGEMENT OF OESOPHAGEAL CANCER

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We conducted a retrospective review of all patients seen with oesophageal cancer at our institution over the last seven years. 225 patients were seen (mean age 49.6y, range 18-85y; 121 males).

**Tumour site:** 72 starting in upper 1/3 (69 squamous cell carcinoma [SCCA], 3 adenocarcinoma [ACA]), 67 mid 1/3 (64 SCCA, 2 ACA, one collision tumour), 86 lower 1/3 or G.O. junction (45 ACA, 34 SCCA, one lymphoma, six miscellaneous).

**Results:** 52 received no treatment (30 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 51.8y. 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 48y. 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 46.4y. 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 years old and many were presented with advanced stage disease. (3) In our country, it is difficult to follow up patients, particularly those from rural areas and with limited means of communication, as evidenced by the large number of patients lost to follow up.

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CHANGES IN MUSCLE UNCOUPLING PROTEIN EXPRESSION IN HUMANS WITH GASTROINTESTINAL ADENOCARCINOMA

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The mitochondrial uncoupling proteins-2 and -3 (UCP-2 and -3) are putative mediators of thermogenesis and energy metabolism and may therefore be of benefit in assisting the decision making process regarding the appropriateness of surgical resection.

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

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**Introduction:** Metastatic carcinoid tumours are difficult to manage. Histopathology generally fails to provide prognostic information. In spite of multidisciplinary approach, including orthotopic liver transplantation (OLT), the recurrence rate is high with a poor prognosis.

**Aim:** To assess 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 and 45 patients had a mean 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. This method can provide an additional parameter for a rational approach to therapy. However this study is very small and a larger number of patients studied prospectively will be needed to confirm our findings.

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METABOLIC THERAPY INHIBITS GENOTOXIC DAMAGE IN REGENERATING INTESTINAL EPITHELIUM

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Adverse effects of many dietary carcinogens are increased in patients with conditions of tissue regeneration. This study tests the hypothesis that metabolic therapy may inhibit DNA damage from dietary carcinogens in regenerating human intestinal epithelium.

**Methods:** Metabolic therapy aimed at (i) inhibition of carcinogen bioactivating enzymes (CYP1A1/1A2) using ellipticine or furafylline and/or (ii) promotion of Glutathione –S transferase (GST) enzymes responsible for carcinogen detoxification, by ethoxyquin or oltipraz.
FEW GASTRO-OESOPHAGEAL MALIGNANCIES ARE IDENTIFIED THROUGH TWO WEEK RULE

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Aim: To identify the proportion of patients diagnosed to have a gastro-oesophageal malignancy through Two Week Rule (TWR) referral.

Methods: All TWR referrals for a suspected gastro-oesophageal malignancy (GOM) were identified from the cancer audit office over a 14 month period (July 2000–August 2001). The number of patients eventually diagnosed to have a tumour through this referral mode was noted. During the same period, the total number of GOMs identified were recorded using a combination of coding and histopathology records. Time from referral to assessment in clinic and time to diagnosis and treatment were recorded for patients referred through TWR and conventional routes.

Results: 199 patients were referred through TWR during the study period. Only 11 patients were subsequently diagnosed to have a malignancy (5.5% of TWR referrals, 29% of total malignancies diagnosed). 27 patients were diagnosed to have a tumour through other modes of referral (emergency admission: 14 (37%), outpatient clinic: 6 (16%), direct access endoscopy: 7 (18%).

Conclusions: Only a minority of patients (5.5%) referred through TWR had a malignancy; the majority (94.5%) had alternative diagnoses. Possible reasons for this includes: (1) referral criteria used in TWR forms may be poor discriminators for GOM (2) over interpretation of alarm symptoms may lead to inappropriate referrals. There is no evidence that the TWR system has resulted in reduction in time to diagnosis and treatment of GOM. However, larger series are required to confirm these findings.

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THE GASTRIC CANCER 5 (GC5) STUDY: ANTIBODY RESPONSE AND SIDE EFFECT PROFILE OF G17DT 500MCG IN POST GASTRIC CANCER RESECTED 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 Corp) 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. Approval was obtained from the local Ethics Committee.

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.

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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: 75–149 cases, band 3: 11–34 cases, and band 4: <10 cases.

In common with other western series oesophageal adenocarcinomas predominate over squamous cell carcinomas. All tumour types were most common in the 65–74 age group and were associated with significant co-morbid disease (40% ASA grades 3–5). The 3293 patients presented to a total of 53 different hospitals, only 1/3 of the patients initially presented to hospital seeing in excess of 75 cases per year. There were differences between regions in terms of the time between referral of cases and final diagnosis. A greater than four week delay occurred in between 13.7% of patients in the region with the shortest waiting times and 31.6% of patients in the longest. Delays were less common in patients initially presenting to band four hospitals—13% of patients waiting greater than four weeks compared with 22% in band one units. There were no differences between the size of the hospital of presentation and the time taken between diagnosis and commencement of treatment. Overall survival at one year was 29%, 32.7% and 34.5% for oesophageal, gastric and gastro-oesophageal junctional, and gastric tumours and at two years: 13.8%, 16.6%, and 20.4% respectively. There was no difference between the size of the hospital of presentation and survival.

Any reorganisation of services must take cognisance of the fact that the majority of patients currently do not present to specialised centres. Patients are not disadvantaged by this and services in smaller units should be supported to ensure continued equity of access.

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GASTRIC CANCER 5 (GC5) STUDY: ANTIBODY RESPONSE AND SIDE EFFECT PROFILE OF G17DT 500MCG IN POST GASTRIC CANCER RESECTED PATIENTS

E.J. Dickson, E. Cowan, R.C. Stuart. University Dept of Surgery, Glasgow Royal Infirmary, Glasgow, UK

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NOVEL METHOD FOR MEASURING NITROSATION POTENTIAL WITHIN LOCALISED REGIONS OF UPPER GI TRACT

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Background: Luminal nitrosation 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 microarray analysis (MD) probes to measure nitrosation at this localised site.

Method: MD probes were perfused with distilled water at 0.15ml/hr. The recoveries of chemicals relevant to luminal nitrosation i.e. nitrite (NO2-), nitrate (NO3-), thiocyanate (SCN-), ascorbic acid (AA) and total vitamin C (TVC) were studied at 37°C at different pH in aqueous solutions and/or gastric juice (GJ). Experiments simulating the gastric milieu, when NO2- 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 ELISA 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 months 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 HIPPURATE ARE USEFUL MARKERS OF ALCOHOLIC CIRRHOSIS
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Both taurine and hippurate are mainly produced by the liver and their excretion rate in the urine could provide us with markers in liver dysfunction. We aimed to evaluate the usefulness of urinary taurine and hippurate levels as markers of cirrhosis.

Materials and Methods: Urine was collected from 40 patients with alcoholic cirrhosis (18 males and 12 females) aged 37-74 (mean age 52.9) and 20 controls (25 males and 15 females) aged 21-68 years (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 0.04 ± 0.005] [p<0.009]. Hippurate excretion index was significantly lower in patients with cirrhosis than controls [0.097 ± 0.016 vs 0.25 ± 0.06] [p<0.014]. If the two values were combined then the results were again highly statistically significant [p<0.000126].

Conclusions: A combination of low hippurate and high taurine excretion is highly significant as a diagnostic tool 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. Glasgow. 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, γ-GT 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 decompressed 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**

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**Background:** Angiotensin II (AngII), the main effector molecule of the RAS, may influence hepatic fibrosis. Functional polymorphisms in components of the RAS (angiotensinogen (Ang), angiotensin converting enzyme (ACE), AngII receptor (AT1R)) which alter gene expression and functional phenotype are recognised. We aimed to determine 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 homoygous for one or none (p = 0.95). Rates (%) of RAS polymorphism for each fibrosis group are shown in the table. On multiple linear regression advanced fibrosis was associated with a history of excess alcohol consumption (p<0.01) and the grade of inflammation on liver biopsy (p<0.001).

**Conclusions:** RAS polymorphisms are not associated with accelerated progression of fibrosis in chronic HCV infection.

**413 THYROID HORMONE (T3) INCREASES THE FUNCTIONAL CAPACITY OF THE INTACT LIVER**

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**Background:** We characterised the time course and magnitude of effect of tri-iodothyronine (T3) as a primary mitogen for the liver in rats. A single [4mg/kg] s/c dose of T3 induces a proliferative response within the liver, which peaks at 24h (7% cell proliferation index) followed by a gradual decline. This increase in cell proliferation results in an increase in liver mass that peaks at 10 days. The 15% increase in liver mass at 10 days (compared to controls) is associated with corresponding increases in total DNA and liver protein levels confirming an increased cell number.

**Aim:** To assess if T3, induced increases in liver mass confer a useful increase in hepatic function, using galactose elimination capacity (GEC).

**Method:** Two groups of rats (n=5) were assigned to either T3, or control (vehicle only) ten days prior to assessing the galactose elimination capacity by: (1) Administering 0.5 ml of 50% galactose via the internal jugular vein approach. (2) A 0.5ml venesection 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 ± 0.6 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*02:01. Tetramers containing the A*0201 restricted core epitope 18–27 showed that three patients with acute resolving hepatitis developed CD8+ T-cells directed at this epitope whereas the patient who developed chronic infection did not. All three patients with detectable CD8+ CTL response developed mutations encompassing the core 18–27 epitope while the remaining seven patients showed genetic stability within the same core region (p=0.01). Previous studies have shown that mutation within the core 18–27 epitope is less efficiently recognised by the prototypic anti-core 18–27 CD8+ CTL response than the wild type sequence, confirming that these variants represent CD8+ CTL escape mutants. However, our study demonstrated that patients with acute HBV infection and CD8+ CTL escape mutants ultimately cleared HBV from serum indicating that the broadly reactive nature of the immune response was capable of clearing such evolving mutants and preventing viral persistence.

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**Abstract 412**

<table>
<thead>
<tr>
<th>Biopsy Ishak Stage</th>
<th>Ang</th>
<th>ACE</th>
<th>ATIR</th>
</tr>
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<tbody>
<tr>
<td>TT (65)</td>
<td>MT/MM (126)</td>
<td>DD (57)</td>
<td>DI/II (144)</td>
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<tr>
<td>0 or 1</td>
<td>36%</td>
<td>64%</td>
<td>29%</td>
</tr>
<tr>
<td>2 or 3</td>
<td>33%</td>
<td>67%</td>
<td>31%</td>
</tr>
<tr>
<td>4 to 6</td>
<td>27%</td>
<td>73%</td>
<td>26%</td>
</tr>
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<td>p=0.881</td>
<td>p=0.824</td>
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www.gutjnl.com
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 urinary excretion of enterally administered lipopolysaccharide and endotoxin was analysed using the Limulus amoebo-cyte lysate [LAL] assay. A stool sample was analysed for calprotectin by ELISA.

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-analyser. Endotoxin was determined using the Limulus amoebo-cyte 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 urinary excretion of endotoxin (p=0.004) 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-analyser. Endotoxin was determined using the Limulus amoebo-cyte lysate [LAL] assay. A stool sample was analysed for calprotectin by ELISA.

Using Spearman’s Rank test there was a positive association between calprotectin tertiles and urinary excretion of endotoxin (p=0.004), aspartate transaminase (p=0.02) and 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. There was no correlation with bilirubin or alanine transaminase. There was no correlation with bilirubin or alanine transaminase.

Association between calprotectin tertiles and alkaline phosphatase (p=0.007), aspartate transaminase (p=0.02) and alanine transaminase (p=0.05). 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.

416 1% of adults homozygous for the C282Y mutation of the HFE gene have been clinically diagnosed with iron overload: evidence from the South Wales haemochromatosis study

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Background: The clinical significance of HFE mutations remains uncertain with a large discrepancy between the frequency of the pre-disposing 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 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 5 S Wales 1 in 147 blood donors are C282Y homozygous. We have calculated that only 1.1% of adult homozygotes have been diagnosed and treated for iron overload.

Conclusions: Genetic screening would detect many thousands of healthy subjects in S Wales. Of the 1% likely to be diagnosed with HH 45% will have moderate to severe iron overload based on established criteria.

The prevalence of portal hypertension (PHT) in primary biliary cirrhosis (PBC)

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Data from our patient cohort suggest that the development of PHT in PBC may be associated with a more adverse outcome than has previously been thought to be the case. Estimation of the overall extent of the morbidity associated with PHT in PBC has been hampered by a paucity of accurate data relating to its prevalence in the patient population. Previous studies (which have shown prevalences ranging from 23–75%) have been limited to case series subject to patient inclusion bias. In order to further quantify the scale of the problem posed by PHT in PBC we studied the prevalence of PBC in a comprehensive cohort of patients defined by geographical residence rather than specific clinical attendance.

A comprehensive and exhaustive case finding exercise was performed to identify all prevalent cases of PBC within the study area. At the census point 166 PBC patients were prevalent within the study area. The point prevalences of portal hypertension, endoscopic varices and 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 incidence rates for PHT (129/312), oesophageal varices (69/312) and variceal haemorrhage development were therefore 75/1000, 33/1000 and 16/1000 patient years at risk respectively.

Conclusions: PHT and its complications are common in patients with histologically advanced PBC. Given the adverse outcome seen with PHT in this disease screening is warranted.

Prognostic accuracy of APACHE III scoring system is greater than that of the conventional Child-Pugh’s score in predicting short-term hospital mortality of non intensive care unit patients with liver cirrhosis

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Objective: The aim of this study was to assess the prognostic accuracy of Child-Pugh’s score (CPS) and Acute Physiology, Age and Chronic Health Evaluation [APACHE] II and III scoring systems in predicting short-term, in-hospital mortality of patients with liver cirrhosis admitted to a gastroenterological medical ward.

Methods: 200 consecutive admissions of 147 cirrhotic patients (44% viral-associated liver cirrhosis, 33% alcoholic, 18.5% cryptogenic, 4.5% both viral and alcoholic) were studied prospectively. Clinical and laboratory data conforming to the Child-Pugh, APACHE II and APACHE III scores were recorded on day one for all patients. Statistical analysis for the prognostic variables was performed by using Hest, receiver operating characteristic [ROC] curves and area under a ROC curve [AUC], non-parametric Wilcoxon test and discriminant analysis.

Abstract 416

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Number with estimated body iron load of ≥4g</th>
<th>Number with estimated body iron load of ≤4g</th>
<th>Number in which body iron not quantifiable</th>
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</thead>
<tbody>
<tr>
<td>HHYY (n=59)</td>
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<td>0</td>
</tr>
<tr>
<td>HDCC (n=11)</td>
<td>6</td>
<td>4</td>
<td>3</td>
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</tbody>
</table>

†Wild type, HHCC; homozygous C282Y, HHYY; homozygous H63D, DDC, etc.
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 0.81 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 stratifies a significantly greater number of patients.

417 HYPERURICAEMIA, GOUT AND CARDIOVASCULAR RISK AFTER LIVER TRANSPLANTATION


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Background: Hyperuricaemia and gout are recognised complications of renal and cardiac transplantation. In contrast the development of hyperuricaemia following liver transplantation has received less attention. Elevated serum uric acid has been cited as an independent risk factor 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 > 28 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.

420 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 81,000 pregnancies – incidence 0.5%. Age ranged from 16-40 years (median 30). There were seven twin and one triplet pregnancies. Sixteen were primiparae 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 45, 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. Symptoms started between 8 and 39 weeks gestation.

Hyperuricaemia was present in 72% and gout was seen in 36% (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). Ureasecholic 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 within 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

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Background: Hepatocellular carcinoma (HCC) is a significant cause of mortality in cirrhotic patients. Its detection at an early stage increases the chance of curative therapy. Clear evidence of survival benefit with surveillance is limited. However, anecdotally, many clinicians undertake some form of surveillance program.

Aim: To evaluate the current practice of HCC surveillance in cirrhosis in the UK.

Methods: 1080 postal questionnaires were sent to the members of the British Society of Gastroenterologists (BSG), excluding radiologists, pathologists and paediatricians.

Results: 525 replied (49%); of these, 120 did not look after adult cirrhotics and were excluded from analysis. Of the 405 remaining respondents, 296 (73%) surveyed for HCC, 123/296 had protocols. Hepatologists and those with a large cirrhotic practice were more likely to survey. 96/296 quoted an age limit (median 70) for surveillance. 107/296 (36%) surveyed all cirrhosis regardless of their suitability for curative therapy; in contrast, 127/296 surveyed only those suitable for liver transplantation or partial hepatectomy. 166/296 (56%) chose to survey all causes of cirrhosis, whereas a smaller group (83/296, 28%) were more selective and surveyed those with Hepatitis B, C, haemochromatosis and alcoholic liver disease. The commonest mode of surveillance was a combination of abdominal ultrasound and alpha fetoprotein, with a wide range of test intervals (3 to 24 months). In those choosing to survey, 130/296 believed it increased survival, while 93/296 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 unsatisfactory 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 reinstated if during follow up, aminotransferases were again high. 110 patients with inactive cirrhosis were the non-treated controls. Time to decompensation and death were recorded. Patients were followed up between 3 and 136 months.

Results: Median time to decompensation was 81 months (95% CI, 45-117 months) and was not different between the two groups.
(p=0.7, Kaplan-Meier analysis). However, variceal bleeding, hepatic encephalopathy and spontaneous bacterial peritonitis were signs of decompensation only in the controls, ascites being the only decompensation sign in the treated group. Overall mortality, although lower in the treatment group just failed to reach significance (p<0.07, 356 patients should be enrolled to reach significance). However, when only liver related deaths were assessed, the survival of the treated patients was significantly better (p<0.05).

**Conclusion:** Hydroxychloroquine treatment reduces liver related mortality in active HCV cirrhosis, despite the fact that the control group were inactive cirrhotics where a more favourable prognosis is to be expected.

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**423 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 hepatitis C and cirrhosis, based on a minimum of 6-monthly serum AFP and ultrasound (US), for a median of 2 years (range 0.5 - 6). 186 US and 662 AFP measurements were undertaken. 11 patients were lost to follow up. 40 (45%) had an elevated AFP and 18 had a suspicious US. 11 patients (12%) developed HCC during surveillance.

**Results:** Of 40 with an elevated AFP, 10 (25%) also had a suspicious US and HCC was identified in 7 of these (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. The level of AFP was again non-discriminatory. Of 49 with a normal AFP, 8 (16%) had a suspicious US and HCC was identified in 3 (6%). 22 CT Scans, 7 MR scans and 11 Angiograms were undertaken in patients who did not have HCC. As a predictive test for HCC, elevated AFP in isolation had a positive predictive value (PPV) of only 0.18, a sensitivity of 0.7 and a specificity of 0.58. In comparison, US had a PPV of 0.8, sensitivity of 0.91 and specificity of 0.89.

**Conclusion:** The incidence of HCC in this group of Hepatitis C cirrhotic patients is high. Surveillance is a considerable burden but the combination of serum AFP and US has traditionally been used for the detection of HCC. However, an elevated AFP in isolation was common, had a poor predictivity for the detection of HCC and led to numerous (expensive) investigations. Restricting surveillance to US alone would be as effective.

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**424 COMBINATION PROPHYLAXIS WITH LAMIVUDINE (LAM) AND HEPATITIS B IMMUNOGLOBULIN (HBIG) PREVENTS GRAFT RE-INFECTION BY HEPATITIS B (HBV)**

V. Lai, E. Elias, K. O’Donnell, D. Mutimer. Liver Unit, Queen Elizabeth Hospital, Birmingham, Edgbaston B15 2TH, UK

Prevention of graft re-infection remains the most important issue in transplantation of HBV infected patients. Re-infection by HBV is almost inevitable if no prophylaxis is given. The course of recurrent infection is aggressive causing sub-acute liver failure or rapid progression to cirrhosis. In the early 90’s, prophylaxis comprised of regular and aggressive causing sub-acute liver failure or rapid progression to cirrhosis. In the early 90’s, prophylaxis comprised of regular and inevitable if no prophylaxis is given. The course of recurrent infection was significant better (p<0.05).

**Conclusion:** The combination of LAM/HBIG prevents HBV re-infection even in high-risk patients.
ROLE OF TECHNICAL VARIABLES IN EARLY SHUNT INSUFFICIENCY FOLLOWING TIPSS FOR THE TREATMENT OF PORTAL HYPERTENSION

S. Balata, H.F. Lui1, A. Helmy1, D. Tripathi1, D.N. Redhead1, P.C. Hayes1.
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Summary: Transjugular intrahepatic portosystemic stent shunt (TIPSS) has increasingly been used for the treatment of complications of portal hypertension. This study evaluated the technical predictors of early shunt insufficiency after TIPSS placement in patients with advanced liver disease.

A retrospective analysis of 399 patients undergoing TIPSS over a period of 9 years between July 1991-July 2000 was carried out. The independent variables included the technical and clinical variables in 87 patients, gastric varices in 52, refractory ascites in 42, portal hypertensive gastropathy in 8 and ectopic varices in 9 patients. TIPSS placement was successful in 383 (96.0%) patients, and failed in 16 (4.0%). The shunt remained patent without assistance in 40 (10.0%) patients and 44 (11.0%) patients developed early shunt insufficiency within 30 days from TIPSS insertion. The univariate association of 21 prognostic clinical and technical variables between patients with early shunt insufficiency and primary patency was tested by the Chi-squared or Wilcoxon rank-sum tests. Multiple logistic regression analysis was utilized to determine the relationship of multiple technical and clinical variables in predicting early shunt outcome.

The two groups were comparable and representative of the whole TIPSS cohort patients. Of the 21 technical and clinical variables, stent diameter, distance of shunt from IVC, duration of the procedure, and portal pressure gradients post TIPSS were independent predictors of early shunt insufficiency.

Based on our analysis, four technical variables at index TIPSS can reliably predict early shunt insufficiency. Total protection from early complications of TIPSS requires awareness of the risk factors and a low threshold maintained for early shunt revision.

CHARACTERISATION OF LIVER INFILTRATING T-CELL ANTIGEN SPECIFICITY IN A MOUSE MODEL OF PRIMARY BILIARY CIRRHOSIS (PBC)


PBC is characterised histologically by damage to the intra-hepatic bile ducts accompanied by a T-cell rich portal tract mononuclear cell (MNC) infiltrate. PBC is characterised immunologically by autoreactive antibody responses 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 autoreactive T-cell responses directed at this antigen in disease pathogenesis. We have recently demonstrated that SJL/J mice can be induced to break down TIPSS and splenic T-cell tolerance to self-PDC, and that this tolerance breakdown is associated with the development of portal tract inflammation and bile duct damage. In this study we set out to characterise the antigen specificity of the infiltrating portal tract T-cells in this model.

Female SJL/J mice of 10–12 weeks were sensitised (n=7) with a mixture of murein 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 were characterised by FACS and primary proliferation. Livers were perfused in situ with collagenase via the portal vein prior to removal. The liver infiltrating mononuclear cell population was isolated by further collagenase digestion and density centrifugation. T-cell responses were characterised as for splenic T-cells.

Female SJL/J mice of 10–12 weeks were sensitised (n=7) with a mixture of murein 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 were characterised by FACS and primary proliferation. Livers were perfused in situ with collagenase via the portal vein prior to removal. The liver infiltrating mononuclear cell population was isolated by further collagenase digestion and density centrifugation. T-cell responses were characterised as for splenic T-cells.

MR-GUIDED LASER THERMAL ABLATION OF PRIMARY AND SECONDARY LIVER TUMOURS


Purpose: To test the hypothesis that MR guided hepatic tumour ablation is (i) safe & feasible and (ii) improves patient survival and (iii) decreases viable tumour voulume.

Methods and Materials: 125 MR guided Laser Thermal Ablations (LTA) have been performed on 40 patients (9 females, 31 males, average age 59.1 years) between 1997 and 2001. The liver tumours include Hepatocellular Carcinoma (HCC, n=19), metastases (n=11, mainly colorectal), carcinoid (n=5) and two benign liver tumours. 3 patients were excluded from follow-up.

Results: Mean survival for all patients was 15.2 months, with an adjusted mean survival of 16 months for HCCs and 15.2 months for metastases. There were three major and five minor post-procedural complications but no deaths. An average of 57% of tumour was ablated as assessed by per-procedural thermal mapping, with an average of 49.4% of tumour ablated assessed by pre and post ablation gadolinium-enhanced MRIs. Average tumour size was unchanged after ablation. In patients with multiple liver tumours ablated tumours grew significantly less than untreated tumours over the same time period (108% compared to 196% growth over an average follow up period of 5.8 months).

Conclusions: MR guided laser thermal ablation of primary and secondary liver tumours is safe and feasible and produces a better survival in patients with HCC than would be expected in untreated patients, as well as a mean survival in patients with metastases at least equal to the longest median survival in untreated patients. Percentage of viable tumour was decreased by a mean of 49.4% per LTA session.
INTRAHEPATIC CHOLESTASIS OF PREGNANCY: AN AUDIT OF SPECIALITY MANAGEMENT OF LIVER BIOPSY IN HEPATITIS C: HAVE WE FOLLOWED NICE GUIDELINES?

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Objective: To audit whether patients with hepatitis C undergoing liver biopsy were subsequently treated according to current NICE guidelines.

Methods: Patients with treatment naïve 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 naïve 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 medically contraindicated in 5 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 anti-viral 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.

AN AUDIT OF SPECIALITY MANAGEMENT OF ALCOHOLIC LIVER DISEASE WITH JAUNDICE

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The development of jaundice in the alcoholic abuser may indicate acute alcoholic hepatitis (AAH) or the progression to end-stage chronic alcoholic liver disease (ALD). These 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. 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 ± 7.9 years with a median admission serum bilirubin of 230.4 ± 184.4 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.

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; 52 male; 56 non-cirrhotic, 13 cirrhotic) had commenced treatment. Genotype distribution was 34 type 1, 38 type 2/3, 2 type 4, 5 type 1 and 6 type 5. Median pretreatment titre was 6.7x10^4 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
E18 EVOLUTION OF HEPATITIS B VIRUS DURING PRIMARY INFECTION

S.A. Whalley, D. Brown, G.J.M. Webster, R. Jacobs, C.G. Teo, V.C. Emery, G.M. Dusheko. Royal Free Hospital, Central Public Health Laboratory, London, UK

To study HBV evolution in vivo, we evaluated over 1 MB-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 ORF: 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 28%). 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.

E19 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 effectively removes albumin bound substances (including bile salts), without the need for anticoagulation. MARS has been shown to be superior to plasmapheresis in patients with acute liver failure. The aim of this study was to determine the efficacy of MARS in patients with chronic liver disease and intractable pruritus.

Patients and Methods: Forty patients with intractable pruritus were studied. Thirty with liver failure were treated with MARS and compared to 10 normal controls. Following MARS treatment, pruritus and QOL scores were assessed. The impact of MARS treatment on pruritus was compared to patients after plasmapheresis and charcoal haemoperfusion.

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 days). 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 asymptomatic and are no longer being considered for transplantation.

Conclusion: Albumin dialysis [MARS] is a novel therapeutic tool which offers safe and effective, but non sustained, relief of pruritus in patients with intrahepatic cholestasis resistant to conventional therapy. The place of this technique in the long-term management of pruritus needs to be further defined.

E22 ABNORMAL VASCULAR FUNCTION IN HEPATIC HAEMOCHROMATOSIS: INVESTIGATING THE "IRON HYPOPOTENSION" CONCEPT

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Background: Iron excess has been linked with development of coronary heart disease. Hepatic 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 (Alx).

Methods: The Alx of patients with Haemochromatosis was recorded as a measure of the arterial stiffness following a 10 hr fast. Age- and sex-matched healthy individuals served as controls.

Results: 10 subjects were recruited to each group (PM:FM). There was no significant difference between the ages of the haemochromatosis and control subjects. 56.6yr v 54.6yr (p=0.62). The Alx 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.

E23 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 transplantation was significantly worse in patients developing PHT (Kaplan-Meier analysis (KMA) p=0.001; 5yr 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; 5ys 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% v 25%).
In the 159 patients developing OV (93 of whom bled), the one-year transplant free survival following OV diagnosis was 63%. Excluding the 34 patients undergoing transplantation (leaving death as the study endpoint) 1-ys was 68%. In the 67 patients developing OV below the age of 65 who did not undergo transplantation 1-ys was 71%.

Conclusion: The development of portal hypertension is associated with adverse outcome in PBC. The risk maps to patients developing varices regardless of bleeding. The one year survival following development of varices is less than that currently being reported for transplanted PBC.

NO ASSOCIATION BETWEEN NOD2 POLYMORPHISMS AND SUSCEPTIBILITY TO, OR PROGRESSION OF, PRIMARY SCLEROSING CHOLANGITIS

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Background: Nod2 is a member of a protein family which regulates apoptosis and NF-kB 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-kB. NF-kB 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 oblitative 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 z’ 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-kB activation, these polymorphisms do not determine the rate of progression or outcome of the disease.

ABNORMAL LIVER FUNCTION TESTS FOLLOWING BONE MARROW TRANSPLANTATION: WHAT IS THE AETIOLOGY AND THE ROLE OF LIVER BIOPSY?

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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 allogeneic and autologous BMTs undertaken in our institution between Jan 1997 and December 1998 were studied. Subsequent liver function tests, the use and indication of liver biopsy and the final cause of liver dysfunction were determined in each case.

Results: 121 patients (63 autologous) with BMT were studied. Abnormal LFTs were found in 71% allogeneic and 33% autologous BMTs. Final diagnoses were made without resorting to liver biopsy and these are shown in the table. Liver biopsy was required in 18 allogeneic and only 1 autologous BMT. 63% biopsies were undertaken greater than 100 days post BMT for persistently abnormal LFTs and these are shown in the table. Liver biopsy was required in 18 allogeneic and only 1 autologous BMT. 63% biopsies were undertaken greater than 100 days post BMT for persistently abnormal LFTs to assess possible GVHD. 16 out of 18 biopsies revealed significant iron overload with only one confirming GVHD. No fibrosis/cirrhosis was found on biopsy. No adverse effects occurred as a result of liver biopsy. In the patients with histological evidence of iron overload, the serum ferritin was also persistently elevated.

Conclusion: Liver biopsy was required in a minority of patients with abnormal LFTs post BMT, with most causes of liver dysfunction diagnosed clinically. Liver biopsy was most commonly undertaken late post BMT in the group with persistently abnormal LFTs in which chronic GVHD was suspected. However, iron overload was the commonest finding in this subgroup; and serum markers of iron excess could determine this.

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PEAK PROPORTION AREA CHANGE (PPAC): A NOVEL METHOD OF THRESHOLD DETERMINATION FOR DIGITAL IMAGE FIBROSIS AREA ESTIMATION ON LIVER BIOPSIES

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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 compare it with the standard interactive method.

Methods: Grey level corresponding to maximum change in pixel counts at 256 grey levels were measured. Differences between scale level representing fibrous tissue is critical. We present and compare it with the standard interactive 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.

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Table showing cause of deranged LFTs

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<tr>
<th>Drugs</th>
<th>Iron XS</th>
<th>GVHD</th>
<th>Sepsis</th>
<th>VOD</th>
<th>Others</th>
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<td>Allogeneic</td>
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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 most commonly undertaken late post BMT in the group with persistently abnormal LFTs in which chronic GVHD was suspected. However, iron overload was the commonest finding in this subgroup; and serum markers of iron excess could determine this.

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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 ~25,000. 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 found only 10/44 (22%) alive, the median survival was 4 months from referral to death.

Conclusions: Symptom guidelines used alone would have missed 16% cancers. Management guidelines suggest a specialist team to identify those liable to benefit from treatment, but the overall outcome is likely to remain poor as comorbidity prevented treatment in many patients.

444 DEPRIVATION CATEGORY AND GASTRO-OESOPHAGEAL 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, GORD and it’s complications.

Methods: A cohort of patients with GORD and Newly diagnosed Barrett’s oesophagus were constructed from a database of patients with reflux symptoms. Deprivation index was obtained by utilising the post code area and sector to calculate the Carstairs Deprivation score (1 least deprived, 6 most deprived). Incidences and putative risk factors were examined.

Results: 658 patients were recruited with symptomatic GORD; when stratified for Carstairs Deprivation Category 1 (least deprived) 20% [14] had Barrett’s oesophagus and 79% [279] 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 consumption [units/week] were further stratified for diagnosis and deprivation category. There was no difference in symptom score according to deprivation category or diagnosis (P>0.05). BMI, Smoking or Alcohol Consumption was equal for diagnosis and deprivation category. There was no difference in symptom score according to deprivation category or diagnosis (P>0.05). BMI, Smoking or Alcohol Consumption was equal for diagnosis and deprivation category. There was no difference in symptom score according to deprivation category or diagnosis (P>0.05).

Conclusions: Ambulant IIEI has a good correlation with pH-monitored reflux events. IIEI is a useful adjunct to pH monitoring in studying reflux, particularly in detecting gas and non-acid reflux events. Manometry is insensitive in detecting pH-RE, but provides information regarding gas, reflux and swallow events. This preliminary study highlights both the potential and the need for further validation and modification of IIEI technique as an ambulatory technique.

446 SELF EXPANDING METAL STENTS: AN AUDIT OF 100 CONSECUTIVE CASES
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Background: Many patients with oesophageal carcinoma present with advanced disease and relief of dysphagia is often the principal goal of therapy. SEMS have become a popular method of palliation but some have expressed concern that quality of life may be less good following SEMS insertion than following ablative methods of palliation. We have therefore undertaken a retrospective audit to identify factors that might predict a less favourable outcome.

Methods: Hospital records were reviewed in 100 consecutive patients in whom an oesophageal SEMS had been placed from June 1998 onwards. Pre-placement clinical characteristics were reviewed in relation to postplacement symptoms and survival.
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, 49 further 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 GOJ (48%) than when in the lower oesophagus 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 Misinformation Highway?

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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. As patients have 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

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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/comorbidity or lost to follow-up. This still left 74 patients under surveillance, but as a result of this audit 21 further patients could be rejected from the programme: 19 had Barrett’s <5cm and 2 were aged over 70 years.

Conclusions: Endoscopic surveillance presents an increasing burden year by year since the cases are diagnosed late. 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


Background: Gastro-oesophageal reflux disease (GORD) is a common condition that has been extensively studied. It is now recognised that patients with laryngeal disease and voice disorders may also suffer from reflux of gastric contents into the upper aero-digestive tract (laryngopharyngeal reflux - LPR). Cellular defence mechanisms are important in protecting the mucosa from the damaging effects of gastric refluxate. It has been suggested that carbonic anhydrase (CA) enzymes may be important in this regard, generating HCO3-, 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 an increase in expression of CA III immunoreactivity. The yield of expression of CA enzymes 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

K. Luritzen, on behalf of the Metropole Study Group, On, Junchard, S. Eklund (introduced by P. Richardson), Odense Hospital, Odense, Denmark; AstraZeneca R&D Mölnndal, Mölnndal, Sweden

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 multi-centre 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 weeks) were randomised to continue treatment with either esomeprazole 40mg od or lansoprazole 15mg od for a further 34 weeks. Follow-up assessments were conducted at weeks 4, 8, 12 and 34, and an endoscopy was conducted at week 34.

Results: The proportion of patients not experiencing an episode of RO (as defined by LA classification) during the 34-week treatment period was significantly higher in the esomeprazole group compared with the lansoprazole group (78% vs 62%, p<0.001). There was no significant difference between the groups in terms of both the duration and severity of the episodes of RO experienced (any, or at the most severe stage of the disease) during the treatment period.

Conclusions: Esomeprazole 20mg od is superior to lansoprazole 15mg od for the prevention of recurrence of RO. Esomeprazole remains efficacious during long-term use with a similar safety profile to lansoprazole.

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and 8 weeks) and symptom-free (i.e. no heartburn or acid regurgitation during the last 7 days of treatment, investigator assessment) patients were randomised to 6 months maintenance treatment with esomeprazole 20mg od or lansoprazole 15mg od. Time to relapse (relapse of RO and/or discontinuation due to symptom recurrence) was analysed using a log-rank test.

Results: Esomeprazole maintained a significantly higher proportion of patients in remission than lansoprazole over the 6-month course of treatment (p<0.0001, ITT analysis-log rank test). After 6 months' treatment, 83% of esomeprazole recipients were in remission compared with 74% of lansoprazole recipients (Life Table estimates). Higher remission rates were consistently achieved with esomeprazole irrespective of baseline LA grade assessed at the beginning of the healing phase. Significantly more patients were free from heartburn in the esomeprazole group compared to the lansoprazole group at 1, 3 and 6 months (p=0.035, Chi-square test). Significant differences at 6 months between esomeprazole 20 mg od and lansoprazole 15 mg od were also observed for control of epigastric pain and acid regurgitation (p<0.05 and p<0.001, respectively, Chi-square test).

Conclusion: Esomeprazole 20 mg od is more effective than lansoprazole 15 mg od for maintaining healed RO and controlling accompanying GORD symptoms.

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### Abstract 452

<table>
<thead>
<tr>
<th>Tooth wear (mean sd) and regurgitation</th>
<th>Teeth wear</th>
<th>Regurgitation</th>
<th>No regurgitation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1.52% (5.9%)</td>
<td>0.65% (1.63%)</td>
<td>P=0.048</td>
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<td>Salivary flow rate (median [range])</td>
<td>0.66 ml/min</td>
<td>1.6 ml/min</td>
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<td>Hoarseness</td>
<td>(0.4–1.1)</td>
<td>(1.1–2.6)</td>
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</tr>
<tr>
<td>No hoarseness</td>
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</table>

543 DOES COOLING SENGSTAKEN-BLAKEMORE TUBES AID INSERTION?

J. Dearden, G. Hellawell, J. Pilling, K. Besherdas, N. van Someren. Chase Farm Hospital, The Ridgeway, Enfield, Middlesex, UK

Introduction: Balloon tamponade using Sengstaken-Blakemore (SB) tubes for oesophageal varices has been in use for almost 50 years. Despite the development of endoscopic techniques, SB tubes still have an important role in the management of variceal bleeding. Standard teaching recommends the use of a cooled SB tube that increases tube stiffness and aids insertion. We surveyed current clinical practice of SB tube use in our region and also assessed whether cooling SB tubes alters the stiffness of the tubes.

Methods: A telephone questionnaire was conducted of gastroenterology registrars and ITU departments in the North Thames region. The current clinical practice and the basis for this practice were determined in each case. The stiffness of SB tubes was measured at 0°C and 23°C by calculating the slope of the plot of load (kg) vs. strain (tube stretch/initial tube length). The time for tube warming from 0°C to 23°C when in stationary air and when in contact with skin was also measured.

Results: Fifty registrars were contacted and twenty ITU departments were surveyed. All ITU departments involved the gastroenterologists in the management of acute variceal bleeds. Eight registrars had never placed an SB tube. The majority of the remainder (93%) used a cooled SB tube. All of the registrars based this practice upon their clinical teaching, and 75% of these registrars thought cooling aided the insertion of the tube. There was no difference in the stiffness of the tubes at 0°C and 23°C. The time for SB tube warming from 0°C to 23°C was 120 seconds in stationary air, and 20 seconds when in contact with skin.
Conclusion: The current clinical practice of trainees for SB tube insertion is to cool the tubes in the belief that this ‘standard’ practice aids tube insertion. We found no change in SB tube stiffness even after cooling to temperatures that would not be achieved during routine insertion. Furthermore, the rapid rise in tube temperature means that tubes approach room temperature by the time they reach the bedside. In the present era of evidence-based medicine the current dogma that SB tubes should be cooled must be discarded.

PHOTODYNAMIC THERAPY (PDT) FOR BARRETT’S OESOPHAGUS: ESTABLISHING THE OPTIMUM DOSE OF 5-AMINOLAEVULINIC ACID (ALA)

C.J. Kelly†, R. Ackroyd†, N.J. Brown†, S.B. Brown†, T.J. Stephenson†, M.W.R. Reed† [introduced by A.G. Johnson], †Academic Unit of Surgical Oncology, †Histopathology, Royal Hallamshire Hospital, Sheffield, UK; †Centre for Photobiology and Photodynamic Therapy, University of Leeds, Leeds, UK

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 68mW/cm² light activation. All patients underwent laser endoscopy under sedation using a balloon applicator and 635nm light at 68mW/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

M. van Blankenstein†, C.P.J. Caygill†, B.J. Johnston†, †Gastroenterology Dept, Rotterdam U.H.; †UK National Barrett’s Oesophagus Registry, Royal Free Hospital, London NW3 2PF; †Lady Sabell Gastrointestinal Unit, Wexham Park Hospital, Slough SL2 4HL, UK

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, O.R. 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.

BARRETT’S OESOPHAGUS, AN INCREASING HAZARD? THE VIEW FROM A UK DISTRICT GENERAL HOSPITAL (DGH)

K.D. Bardhan, C. Royston, P.J. Willemsen, S.J. Haggie, R.B. Jones, J.C. Cooper, L. Harvey, T. Marshall, D.N. Slater. Rotherham General Hospitals NHS Trust, Moorgate Road, Rotherham S60 2UD, UK

Introduction and Aim: We present our 20 year experience of Barrett’s oesophagus identified from the open access endoscopy programme 1977–1996 and followed up in our DGH until 31.12.00. Patients [pts], methods Barrett’s was diagnosed by histology or visually if >3cm length. Pts were treated with H2RA or PPI and followed by endoscopy and biopsy or by clinical means alone (including telephone survey) if elderly or unwilling.

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 presented with, and all 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.

TRANSFECTION INTO AND EXPRESSION OF P53 IN THE HUMAN OESOPHAGUS: AN EX VIVO STUDY

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Background: Oesophageal cancers have a poor prognosis; treatment of these cancers by chemotherapy, radiotherapy and surgery improves this in only a small minority. Mutations in the p53 gene are common in oesophageal cancer and 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.

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<table>
<thead>
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<th>Age bands</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
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<tbody>
<tr>
<td>Males</td>
<td>0.16</td>
<td>1.15</td>
<td>2.05</td>
<td>3.93</td>
<td>4.05</td>
<td>4.89</td>
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<tr>
<td>Females</td>
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<td>0.22</td>
<td>0.75</td>
<td>0.97</td>
<td>1.96</td>
<td>3.75</td>
<td>2.44</td>
</tr>
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</table>
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 control.

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.

Abstract 456

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<tr>
<td>Reflux¹</td>
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<td>1587</td>
<td>2381</td>
<td>3812</td>
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<td>Barrett’s²</td>
<td>43(6%)</td>
<td>53(3.3%)</td>
<td>121(5.1%)</td>
<td>151(4%)</td>
<td>368(4.3%)</td>
</tr>
</tbody>
</table>

¹Newly developed GORD ²Barrett’s at presentation or at follow-up

Investigation of bile acid composition in gastric juice samples from patients with GORD

J. Darrogh¹, P.E. Ross¹, N.M. Kennohan¹, P.W. Dettmar³. ¹Ninewells Hospital and Medical School, University of Dundee, UK; ²Reckitt Benckiser Healthcare Ltd, Hull, UK

Pre-malignant Barrett’s oesophagus and reflux oesophagitis are associated with the reflux of stomach contents into the lower oesophagus. Although the role of acid and pepsin as damaging agents within this refluxate has been well established, attention is now becoming focused on the potential effect of bile acids. This study aims to determine the bile acid composition of refluxate in patients with GORD, so that an in vitro model can be set up to determine the effect of bile acids may have, in inducing cellular injury to oesophageal epithelium.

Methods: Gastric juice samples were obtained from 170 patients with gastro-oesophageal reflux disease (112 with oesophagitis and 58 Barrett’s oesophagus). The bile acid composition was determined by gas chromatographic analysis.

Results: Conjugated bile acids were detected in 95% of samples with concentrations ranging from 1.2 umol/l to 6.4 mmol/l, however only 11 samples contained concentrations exceeding 1 mmol/l. Mean concentrations of the primary bile acids, cholate and chenodeoxycholic acid were calculated to be 119 mmol/l and 112.1 mmol/l respectively, however the mean concentration of the secondary bile acid deoxycholic acid was 63.2 mmol/l. In comparison a much lower mean concentration of lithocholic acid, a particularly toxic bile acid, was found (mean concentration = 17 mmol/l). Sixty four percent of patients had unconjugated bile acids present in their gastric juice with only 18 patients having concentrations in excess of 20 mmol/l.

Conclusions: Bile acids are normally present in the gastric juice of patients with both Barrett’s oesophagus and oesophagitis. For both groups conjugated bile acids are the predominant species, with primary bile acids being in excess of secondary. The presence of toxic bile acids within gastric juice suggests that they may have a role in the pathogenesis of GORD. Furthermore the present data have indicated appropriate concentrations of individual bile acids for investigating the effect of bile acids on apoptotic and stress responses in established oesophageal cells lines.

This research was funded in part by Reckitt Benckiser Healthcare (UK) Ltd, Hull, UK.

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

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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.

OESOPHAEGAL ACID EXPOSURE AND PROTON PUMP INHIBITOR REQUIREMENTS IN SCLERODERMA

M.J. Gibbons, R.G.P. Watson, B.T. Johnston. Department of Medicine, Royal Victoria Hospital, Belfast, Northern Ireland

Gastro-oesophageal reflux disease (GORD) is a cause of significant morbidity in scleroderma (SSc). Proton pump inhibitors (PPI) are frequently used yet information is limited regarding their effect on oesophageal acid exposure in SSc.

The aim of this study was to examine the nature of pathological oesophageal acid exposure in SSc and, in addition, to evaluate PPI requirements.

SSc patients with reflux symptoms and who fulfilled ACR diagnostic criteria were recruited. Subjects underwent 24-hour ambulatory oesophageal pH monitoring. The following pH parameters were recorded: percentage of study time at pH<4 for the total, erect and supine periods, the number of long reflux events (>5 minutes) and the duration of the longest reflux event. Those subjects with exposure times above previously determined normal values were commenced on PPI therapy. Treatment was sequentially increased, with repeat pH monitoring after each increment, until a treatment endpoint of normalisation of acid exposure was reached.

Twenty-two subjects were recruited. Fourteen (64%) had an abnormal oesophageal pH profile. The median % of the total study time at pH<4 was 11.3% (normal <4.9), for the erect period 11.9% (normal <6.2) and for the supine period 4.1% (normal <1.2). The median
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 remained normalised on high dose twice daily therapy.

The majority of SSC patients with reflux symptoms have pathologic 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**

R. Shah, A. Lim, S. Jones. Epsom General Hospital, Epsom, Surrey, UK

Expanding metal oesophageal stents are widely used for palliation of oesophageal cancer. These stents are designed to be inserted by endoscopy with fluoroscopic guidance. This need for X-ray can be limiting for endoscopists in centres with limited or no fluoroscopic services. Even with fluoroscopy, external marking of the position of the tumour can be inaccurate and internal marking of the tumour can be time consuming.

We have used a modified deployment technique, guided by direct endoscopic visualization without the need for fluoroscopy. Microvasive (Boston Scientific) stents were used. The proximal 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 visualization of the proximal end of the stent and the proximal end of the stricture.

We inserted 47 stents in 43 patients with obstructive malignant oesophageal strictures; 27 male, mean age 79 years (range 44–97). Histologically there were 22 adenocarcinomas, 7 squamous carcinomas, 7 undifferentiated cancers and 1 severe dysplasia. Covered and uncovered stents of 10, 15 and 17cm were used.

In 4 patients with almost complete stenosis, the stenosis was first dilated but the stents were inserted by the method described above. There were no cases of malposition and there were no immediate complications of stent insertion.

In our experience, stent insertion by direct endoscopic visualization was technically simple and successful. We found it simpler and more accurate than techniques that involve internal or external marking of the tumour followed by fluoroscopy. This technique is of particular use in centres with limited or no fluoroscopic services.

**462 THE BARRETT'S OESOPHAGUS DATABASE FOR SHEFFIELD (BODS)**

M.D. Gough, R.A. Ackroyd, N. Bird, A.W. Majeed (introduced by A.G. Johnson). Academic Surgical Unit, University of Sheffield, K Floor, Royal Hallamshire Hospital, Glossop Rd, Sheffield S10 2JF, UK

**Aims:** To develop a database for patients with Barrett’s Oesophagus, which would aid clinical follow up, monitoring of disease progression and facilitate research studies.

**Methods:** We have developed a Barrett’s Oesophagus Database for Sheffield patients (BODS). This has been produced in Microsoft Access® and employs a drop down menu system to facilitate data entry and allows for the recording of patient demographics, relevant drug and past medical history, endoscopy summaries, 24 hour pH and manometry studies, histology, treatment, and follow up.

**Results:** Over 300 patients have been entered into BODS, we have found it to be user friendly and versatile e.g., the operator can choose an endoscopic surveillance interval for each individual patient, complete reports of a patients record with endoscopic findings and histology results can be easily produced. The query tool will automatically calculate future endoscopy intervals and dates thereby reducing clerical errors.

**Conclusions:** BODS is proving to be an effective tool in both the clinical and research settings and a rival to other systems such as Endoscribe™. In the future, it could be used in other hospitals and modifications could allow flexibility to include other conditions. A multimedia presentation will demonstrate data entry, analysis, and report production.

**463 TOWARDS SELECTIVE MUCOSAL ABATION FOR BARRETT’S OESOPHAGUS: STUDIES OF PHOTODYNAMIC THERAPY USING mTHPC IN THE NORMAL RAT COLON**

N.F. Jamieson, A.J. MacRobert, S.G. Bown, L.B. Lovat. National Medical Laser Centre, Department of Surgery, Royal Free & University College School of Medicine, London, UK

**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 strictures.

Meso-tetrahydroxyphenylchlorin (mTHPC - GunataNova) is a potential 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 were performed in Wistar rats given mTHPC (0.1 mg/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 colon was treated at laparotomy using a diffuser fibre and 652nm light. The light dose was 3, 9 or 27l 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 to 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 still seen. 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, E. Ebrahim, E. Townsend¹, M. Burke¹, M.R. Thursz. Faculty of Medicine and Histopathology, Imperial College, St Mary’s Campus; ¹Harefield 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 described as 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), S2F11 (β2), 6F12 (β3), B8B11 (β2), MAb1920 (γ1), MAb1922 (α2), MAb1924 (α3), MAb2041 (β1), MAb19562 (γ2) 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 γ2 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 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 α1 and γ2 laminin chains may have an important role in Barrett’s metaplasia in the oesophagus.