Abstracts

Inflammatory bowel disease free papers 001–012

001 THE LIFE EXPECTANCY OF IBD PATIENTS IN THE UK USING LIFE TABLE METHODOLOGY

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Background: We have recently shown that there may be as much as a fourfold increase in risk of death in young adults with Crohn's disease,[1] but that in absolute terms this equates only to a small increase in the rate of death. This may be easier to understand if it is presented in terms of life expectancy.

Methods: We selected subjects in GPRD with IBD and up to five matched controls for each. We derived the date of deaths. We calculated the absolute risk of death within five year age bands and derived life tables to enable the calculation of life expectancy for all IBD, for UC, and for Crohn's disease.

Results: We included 16550 IBD cases with 1047 deaths and 82917 controls with 3758 deaths. An abridged life table for all IBD. The loss of life expectancy was 3.5 years at 15 years of age, and fell thereafter. This effect was greater for Crohn's disease (life expectancy at age 15 5.0 years lower than in controls) and lower for UC (life expectancy at age 15 2.3 years lower than in controls).

Conclusions: IBD does reduce life expectancy by a small number of years. This effect is far smaller for older patients. The 3.5 year difference between cases and controls is less than half as large as that between professionals and unskilled manual workers in the UK.

1. **Card TR**, *et al. Gastroenterology*, in press.

002 ORAL CONTRAST ULTRASONOGRAPHY IN THE ASSESSMENT OF SMALL INTESTINE CROHN'S DISEASE, A PROSPECTIVE COMPARISON WITH CONVENTIONAL ULTRASOUND, *X* RAY STUDY, AND COLONOSCOPY

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Background and Aim: Despite the usefulness of bowel US in intestinal diseases, barium enteroclysis (BE) remains the gold standard technique for assessing patients with CD involving the ileum/jejunum. A novel method, using oral non-absorbable solutions containing polyethylene-glycol (PEG), has been recently proposed in order to improve small bowel US visualisation. We evaluated the accuracy of oral contrast US in localising CD lesions, their extent within the bowel, and detecting luminal complications by comparison with BE and colonoscopy.

Material and Methods: 102 consecutive patients with proven CD, having undergone complete *x* ray (including BE), and endoscopic evaluation, were enrolled in the study. Each US examination, before and after the ingestion of 350–800 ml of a PEG 3350 solution, was performed independently by two sonographers unaware of the results of other diagnostic procedures. The accuracy of conventional and contrast enhanced US in detecting CD lesions and complications as well as the extent of bowel involvement was determined. Interobserver agreement between sonographers with both US techniques was also estimated by means of kappa statistics.

Results: After PEG ingestion satisfactory distension of the intestinal lumen was obtained in all patients, with a mean time to reach the terminal ileum of 31.4 (SD10.9) min. Overall sensitivity of conventional and contrast enhanced bowel US in detecting CD lesions were 92.9% and 96.4%, respectively. The correlation coefficient between US and radiographic extent of ileal disease was $r_1 = 0.78$ ($p<0.001$) before and $r_2 = 0.93$ ($p<0.001$) after PEG ingestion, r_1 *v* r_2 $p = 0.02$. Sensitivity in detecting strictures was 77% for conventional US and 86% for contrast US. Overall interobserver agreement for disease location and extension within the small bowel substantially improved after PEG ingestion (0.88 and 0.59 before, 0.98 and 0.76 after oral contrast, respectively).

Conclusions: Oral contrast bowel US is quite comparable to BE in defining anatomic location and extension of CD and superior to conventional US in detecting luminal complications, also reducing interobserver variability between sonographers. It may be therefore regarded as the first imaging procedure in the diagnostic investigation and follow up of patients with small bowel CD.

003 LONG TERM FOLLOW UP OF UC PATIENTS TREATED WITH CYCLOSPORIN—7 YEAR EXPERIENCE

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Background: Cyclosporin (CyA) Rx has emerged as an important agent for rescue Rx in acute severe UC. High 1 year relapse rates advocate a limited role of this treatment in light of CyAs s/e profile. Some advocate CyA only as a stopgap to surgical Rx. There are few data available on longer follow up of these patients.

Aim: To examine long term remission in UC patients who required CyA rescue Rx, analyse surgery rates after successful CyA Rx, and collect information on s/e.

Methods: A retrospective database of UC patients requiring CyA Rx (1996–2003) was constructed. Patients were started on CyA on the basis of their day 3 CRP+/− stool frequency, or after 7 days of intravenous steroid. Other data included disease extent, indication, dose, duration, route of administration, and s/es. Time to first relapse+surgery data were collated.

Abstract 1

	IBD			Controls		
Age group	Deaths observed	Mortality rate/ 1000 years	Life expectancy	Deaths observed	Mortality rate/ 1000 years	Life expectancy
15	1	1	**56.5**	2	0.4	**60.0**
20	3	1.1	**51.8**	3	0.2	**55.1**
25	6	1.3	**47.1**	12	0.5	**50.2**
30	10	1.6	**42.4**	19	0.6	**45.3**
35	13	2.1	**37.7**	26	0.9	**40.5**
40	18	2.8	**33.1**	37	1.2	**35.6**
45	29	4.4	**28.5**	82	2.5	**30.8**
50	46	8.2	**24.1**	99	3.5	**26.2**
55	42	9.5	**20.0**	159	7.1	**21.6**
60	70	16.4	**15.8**	211	9.9	**17.3**
65	124	31.2	**12.0**	395	19.5	**13.1**
70	167	48.2	**8.6**	560	30.7	**9.1**
75	169	65.8	**5.2**	696	49.5	**5.2**
80	349	136.9	**1.3**	1457	99.6	**1.0**

Results: Total 76 UC patients (33F:43M, LS = 26, pan = 22, distal = 28) received CyA, median follow up 2.9 years (range 0.2–9.0 years). 54 patients received IV CyA (median duration 4 days, range 1–7 days), 22 received oral CyA initially because of low cholesterol or Mg^{2+}(median duration 4 weeks, range 0.1–80 weeks). Median CRP and stool freq at day 3 was 20 (range 6–285) and 6 (range 1–22) respectively. 20 patients (26%) failed to achieve initial remission and underwent surgery and 1 patient died post-op from small bowel perforation. 56 patients (74%) went into remission after initial CyA therapy, 23 patients (42%) retained their colon at 80 weeks follow up, 6 patients (12%) were relapse free by 54 wks. S/es were common (none life threatening) and CyA was stopped in 4 patinets because of s/e. KM survival analyses compared time to first relapse and surgery in 5 patient groups: 1) IV CyA $<$5 days *v* $>$5 days; 2) patients who started CyA after $<$5 days of intravenous steroids *v* $>$5 days of intravenous steroids; 3) patients taking AZA *v* patients no AZA; 4) patients given intravenous CyA *v* those given initial oral; 5) patients $>$12 weeks oral CyA *v* $<$12 weeks oral CyA. There were no significant differences in time to first relapse or surgery for groups 1, 2, 3, and 5. In group 4, patients who were given oral CyA had improved survival (time to first relapse/surgery) compared to those treated with intravenous CyA.

Conclusions: This confirms previously data on initial response to CyA therapy. These long term data confirm efficacy and safety (no patient took PCP prophylaxis) of CyA (4 discontinued due to s/e), since 42% patients retain their colon after 80 weeks f/u. Oral CyA appears to be at least as efficacious as intravenous CyA.

004 PROSPECTIVE 2 YEAR STUDY OF 5-AMINOSALICYLATE NEPHROTOXICITY IN THE UK

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Aims: This 2 year prospective study assessed the epidemiology of nephrotoxicity associated with 5-amino-salicylate (5-ASA) use in patients with IBD in the UK from January 2000 to December 2002. The 1298 names in the British Society of Gastroenterology database reported new cases on a monthly basis. All 290 consultant members of the Renal Association reported cases every 6 months.

Methods: Demographic information, treatment details, type/extent of IBD, duration/dose of 5-ASA prior to nephrotoxicity, renal function (pre 5-ASA, at diagnosis and after recovery), and renal biopsy histology were collected. Estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease formula was used (to overcome differences in creatinine due to age, sex, and ethnicity). Cases reported by gastroenterologists and nephrologists were cross referenced to avoid duplication.

Results: 59 new cases, median age 52 years (M:F ratio 47:12), Ulcerative colitis 31, Crohn's 15, indeterminate IBD 7, not stated 6. Mesalazine was the commonest drug implicated. Median time to diagnosis from starting 5-ASA was 41 months (1–96). Mean eGFR pre-treatment was 74.7 ml/min, at diagnosis 29.4 ml/min (creatinine range 92–1361 μmol/L), and mean recovery eGFR 47.3 ml/min. 16/19 renal biopsies showed tubulointerstitial nephritis. Recovery of renal function was more likely in patients treated for $<$12 months (n = 10, mean recovery eGFR 66.1 ml/min) *v* $>$12 months (mean recovery eGFR 44.1 ml/min, p = 0.015). There was no correlation between 5-ASA dose and degree of renal impairment; patients with Crohn's and UC with respect to peak or recovery eGFR; disease extent; degree of renal impairment; and use of immunosuppressant or other drug therapy. Renal function did not recover in 4 patients (1 died), 24 were left with significant renal impairment.

Conclusions: Nephrotoxicity is a serious complication of 5-ASA therapy. Regular monitoring of renal function during treatment may allow earlier detection, particularly during the first year of therapy. Based on an IBD prevalence in the UK of $412/10^5$ with ~50% on treatment (Rubin *et al* APT 2000), we estimate that clinical nephrotoxicity occurs in about 1 in 4000 pts/yr taking 5-ASA therapy.

005 THE CLINICAL COURSE OF ULCERATIVE COLITIS AFTER ORTHOTOPIC LIVER TRANSPLANTATION FOR PRIMARY SCLEROSING CHOLANGITIS

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Background and Aims: Primary sclerosing cholangitis (PSC) is strongly associated with ulcerative colitis (UC). In patients with advanced liver disease secondary to PSC, orthotopic liver transplantation (OLT) remains the only therapeutic option. Previous reports on the course of UC following OLT are conflicting. We documented the course of UC prior to and following OLT in patients with PSC/UC, in the Scottish Liver Transplant Unit between November 1992 and March 2003.

Methods: 26 patients with UC/PSC underwent OLT (16 males: 10 females, mean age of OLT 46.8 years). Six patients were excluded from further analysis (1 patient death at day 7 post-OLT, 1 patient developed UC post-OLT, and 4 patients pre-OLT colectomy). Median follow up prior to and following OLT was 11.67 and 4.33 years, respectively.

Results: *Relapses:* significant increase in relapses/year post OLT compared with pre OLT (1.11 ± 1.0 *v* 0.30 ± 0.35, p = 0.002). 56% (9/16) were on prednisolone and 37.5% (6/16) were on ⩾10 mg prednisolone at time of relapse. *Corticosteroid use for UC post-OLT*: more oral or intravenous corticosteroid courses/year were required for treatment of active UC post OLT compared with pre OLT (0.76 ± 0.98 *v* 0.13 ± 0.27, p = 0.007). *Corticosteroid dependence*: 20% of patients (4/20) became corticosteroid dependent post OLT. Only one patient was corticosteroid dependent prior to OLT. Colectomy post-OLT: 35% (7/20) patients underwent colectomy post OLT, 4 for severe disease, 1 for adenocarcinoma, and 2 for severe dysplasia. *Neoplasia*: 3/20 patients developed colonic adenocarcinoma (1) and moderate-severe dysplasia (2). Gastrointestinal lymphoma, and Bowen's disease were diagnosed in 2 patients of the PSC/UC group who had undergone colectomy pre OLT.

Conclusions: Despite immunosuppression, UC in patients after OLT for PSC/UC follows a more aggressive clinical course after OLT and is associated with a high rate of neoplasia.

006 IMMUNE CELL DYSFUNCTION IN PATIENTS WITH ULCERATIVE COLITIS (UC) AND THE INTERREALTIONSHIP WITH QUORUM SENSING MOLECULES PRODUCED BY GUT BACTERIAL FLORA

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Introduction: Deregulation of gut associated lymphoid tissue (GALT) is postulated to be important in the pathogenesis of UC. Data from animals suggest that bacteria or their products may play a role in GALT deregulation. QSMs are bacterial products, able to sense population density and switch on virulent genes in the gut. Their role in UC has not been documented.

Aims: (1) To determine the presence of QSMs in situ and systemically in patients with UC; (2) to evaluate deregulation of dendritic cells (DCs) and T cells and interrelationship with QSMs.

Methods: UC patients (n = 16) and controls (n = 10) were recruited into the study. Expression of co-stimulatory molecules (CD86) and adhesion molecules (CD40) on colonic DCs (CDCs) and on blood DCs (BDCs) were studied. Modulating effect of QSMs on these markers was evaluated. The effects of QSMs on DCs induced proliferation of T cells (MLDCR) and superantigen induced activation (CD69 & HLADR) of blood T cells were investigated. Qualitative assay of QSMs in the serum and colonic washout was done using thin layered chromatography. The cytokine productions of MLDCR were analysed using cytokine bead array method.

Results: Phenotype of BDCs was identical in UC patients and controls. Expression of CD86 in the CDC of controls were higher than patients (p = 0.008). QSMs in patients down regulated CD86 on BDC ($p<0.05$). T cell activation (CD69) was inhibited by 100 μM QSMs in patients and controls ($p<0.02$); there was no intergroup difference. QSMs were detected in the circulation of patients and controls. MLDCR had similar levels of activity in patients and controls. In both patients and controls QSMs inhibited MLDCR at 10, 100, and 1000 μM ($p<0.001$). In patients and controls QSMs suppressed the production of IFN-γ, TNF-α, IL-10 ($p<0.05$), and increased production of IL-4 ($p<0.04$).

Discussion and Conclusion: We have demonstrated for the first time the presence of QSMs in blood; colonic washouts were negative, but faecal samples positive. QSMs significantly inhibit DCs and T cells in vitro. They also skew the immunological reaction towards T helper 2. These findings suggest a possible role of these molecules in UC.

007 LOCALISATION OF EOSINOPHILS TO DIFFERENT SUBSPECIES OF NERVES IN INFLAMMATORY BOWEL DISEASE

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Introduction: The role of the eosinophil, which is a common inflammatory cell in inflamed gastrointestinal mucosa in inflammatory bowel disease (IBD) is uncertain. Many of the symptoms of IBD are due to neural dysregulation, including increased mucous production and dysmotility. We hypothesised that an interaction between eosinophils and nerves may explain how inflammation is related to neural dysfunction in IBD. The aim of this study was to determine the interaction of eosinophils with nerves in IBD, and to define the type of nerves involved.

Methods: Using formalin-fixed paraffin embedded tissue from patients who had previously undergone colonic resection for intractable symptoms of IBD, the inter-relationship of eosinophils and enteric nerves was assessed. Using double immunohistochemical staining techniques, eosinophils were identified using an antibody to major basic protein (MBP), and nerves were subtyped using antibodies to S100, substance P, nitric oxide synthase (nNOS), and choline acetyltransferase (ChAT).

Results: Eosinophils selectively localise to nerves in the mucosal layer of patients with Crohn's disease ($p<0.001$) and ulcerative colitis ($p<0.01$). Eosinophils also selectively localise to nerves in the muscle layer of patients with both Crohn's disease and UC, although to a lesser degree in UC ($p<0.05$). Furthermore, eosinophils localise to specific nerve subtypes, namely substance P and ChAT containing nerves but not nNOS containing nerves.

Conclusion: Eosinophils localise to specific nerve subtypes in patients with active IBD. Interactions between these cells may influence both nerve and eosinophil function.

008 PANETH CELLS IN CROHN'S DISEASE—EFFECT OF NOD2/CARD15 VARIANTS

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Introduction and Aims: Crohn's disease (CD) is a chronic inflammatory gastrointestinal disorder characterised by an abnormal mucosal immune response, probably triggered by components of the intestinal bacterial flora, in genetically susceptible hosts. NOD2/CARD15 is the first susceptibility gene identified in CD and is thought to interact with bacterial muramyldipeptide (MDP) intracellularly, leading to activation of the NFκB pathway. NOD2 is constitutively expressed in monocytes and in Paneth cells in the small intestine, possibly explaining why NOD2 mutations are particularly associated with CD of the small intestine. Paneth cells are specialised secretory epithelial cells located at the base of crypts of Lieberkühn in the small intestine and produce important antibacterial proteins such as lysozyme, secretory phospholipaseA2 ($sPLA_2$), and α-defensins. In this study we investigated Paneth cell morphology and gene expression in CD in relation to the NOD2 genotype.

Methods: PCR, restriction fragment length polymorphism, and sequencing were used to identify patients with NOD2 mutations. Terminal ileal surgical resection specimens of these patients were then used for immunohistochemistry and western blot analysis to detect expression of lysozyme, $sPLA_2$, and human α-defensin 5 (HD5).

Results and Conclusions: Immunohistochemistry confirmed expression of all major Paneth cell antimicrobial products, including lysozyme, $sPLA_2$ and HD5, regardless of the NOD2 genotype. Using lysozyme, the most abundantly expressed Paneth cell protein as a marker, we found an overall increase in Paneth cell numbers per crypt in the NOD2 mutant homozygous group compared with heterozygous and wild type patients. In addition, the distribution of Paneth cells in patients with NOD2 mutations was abnormal. These data indicate a clear effect of NOD2 mutations on aspects of Paneth cell differentiation and function in terminal ileal CD, although there is no indication of an absolute decrease in the production of antibacterial proteins and peptides.

009 TOLL LIKE RECEPTORS 2 AND 4 ARE UPREGULATED ON HUMAN LAMINA PROPRIA DENDRITIC CELLS IN INTESTINAL INFLAMMATION

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Introduction: Dendritic cells (DC) are antigen presenting cells present in the intestinal tract that sample microbial products within the gut lumen and play a central role in linking innate and adaptive immunity. Recognition of microbes by DC is in part by toll like receptors (TLR). We assessed the expression of TLR2, which interacts with peptidoglycan and lipoteichoic acid from Gram positive bacteria, and TLR4, which is required for recognition of LPS on intestinal DC from patients with inflammatory bowel disease and controls.

Methods: Mononuclear cells were obtained by collagenase digestion of endoscopic biopsies from Crohn's disease (7), ulcerative colitis (19), and controls (16). DC were identified in intestinal cells and blood by multi-colour flow cytometry. Cell surface TLR expression was quantitated using subtraction software.

Results: In agreement with their known responses to microbial ligands, blood myeloid DC expressed surface TLR2 (92.1 ± 0.6% positive DC) and TLR4 (25.4 ± 5.3%) but the plasmacytoid subset expressed neither TLR. In contrast, there was little or no expression of either TLR2 or TLR4 on CD11c+colonic or ileal DC from controls. However, there was significant upregulation of both TLR2 and TLR4 expression on colonic DC in ulcerative colitis (TLR 2 54.3 (SD 4.9)%; TLR 4 35.5 (SD 8.3)%) and Crohn's disease (TLR 2 42.1 (SD 8.1)%; TLR 4 43.9 (SD8.6)%). Enhanced TLR expression on DC was confined to inflamed tissue when paired samples of inflamed and non-inflamed tissue from the same individual were compared.

Conclusions: There is low expression of TLR in normal intestinal DC which may contribute to the role of DC in tolerance and their ability to coexist with potentially activating commensal flora. Increased TLR expression by DC is associated with intestinal inflammation and may contribute to the altered immune response to microbial products.

010 VASCULOGENESIS IN COLITIS: BONE MARROW STEM CELLS ENGRAFT AND TRANSDIFFERENTIATE TO FORM VASCULAR CELL LINEAGES

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We have previously shown that transplanted bone marrow stem cells (BMSC) contribute to various cell lineages in the diseased colon including myofibroblasts, fibroblasts, smooth muscle (SM) cells, and epithelial cells. We now show venules containing BMSC derived SM cells, endothelial cells, and pericytes in the inflamed mouse colon, highlighting the role of BMSC in vasculogenesis in tissue regeneration.

Lethally irradiated female mice were rescued by a bone marrow transplant (BMT) from male donors. Colitis was induced by intrarectal injection of trinitrobenzene sulfonic acid (TNBS) 6 weeks post-BMT, and colons were analysed 1–14 days later. In situ hybridisation for the Y chromosome was combined with immunohistochemistry for specific antigens (alpha smooth muscle actin [SMA], ICAM-1, and EphB4) to identify transplanted cells and determine their phenotype.

We identified EphB4-immunoreactive venules in inflamed regions containing endothelial, vascular SM cells, and pericytes that displayed a Y chromosome and were therefore derived from transplanted BMSC. Pericytes and vascular SM lining cells, delineated by morphological criteria, were SMA-positive, and endothelial cells expressed ICAM-1.

We believe this is the first report of BMSC regulation of vasculogenesis in the diseased gut. It is possible that transplanted BMSC engraft within existing venules and promote regeneration by angiogenesis, or alternatively, that BMSC form entire new venules by neovasculogenesis. This study demonstrates the importance of BMSC in tissue repair in diseases such as inflammatory bowel disease (IBD), and provides a potential mechanism for the beneficial effects of allogenic BMT in IBD.

011 ASSOCIATION OF EPIDERMAL GROWTH FACTOR MODULE CONTAINING MUCIN LIKE HORMONE RECEPTOR 3 (*EMR 3*) MUTATION WITH SUSCEPTIBILITY AND PHENOTYPE OF CROHN'S DISEASE

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Backgrounds: Linkage of Crohn's disease (CD) to chromosome 19p13 has been identified in a Canadian IBD population and confirmed in British Caucasians. *EMR3* maps to this region, belongs to a class B seven-span trans-membrane (TM7) receptor family,

and displays a predominantly leukocyte restricted expression pattern, with highest levels in neutrophils, monocytes, and macrophages. It may play a role in myeloid–myeloid interactions during immune and inflammatory responses. We postulate that *EMR3* is a good positional and also a functional candidate gene for IBD.

Methods: The mutations of *EMR3* were first detected by direct sequencing and the association of these polymorphisms with IBD investigated by using independent case control studies and transmission disequilibrium tests (TDT). Genotyping was performed with Sequenom and PCR-SSP in 380 UK Caucasians with CD, 379 with UC, and 754 healthy controls.

Results: 9 new variants of EMR3, 2 of which are exonic with an amino acid change (E127Q G/C and A236V G/A), were identified. Of 6 SNPs selected for genotyping, only E127Q showed strong associations to the clinical manifestations of CD but weak associations to UC in case control studies. Homozygosity for the mutant Q127Q-C/C was significantly associated with susceptibility to ileal CD (p = 0.006, OR 1.9, 95% CI 1.22–2.97), and this effect was particularly strong in patients with pure ileal disease (p = 0.0006, OR 2.8, 95% CI 1.66–4.71), fibrostenosing disease (p = 0.002, OR 2.09, 95% CI 1.34–3.27) and surgery for stenotic disease (p = 0.005, OR 2.03, 95% CI 1.26–3.28). The wild type E127E-G/G appeared to be protective for UC patients (p = 0.02 OR 0.73, 95% CI 0.57–0.94). The susceptibility to CD was further confirmed by TDT (p = 0.02). No evidence of epistasis between *EMR3* and *CARD15/NOD2, IBD5*, and *ICAM1* was demonstrated.

Conclusions: *EMR3* may be a susceptibility gene for CD, independent of *CARD15/NOD2*. The biological significance of its mutations in immunopathogenesis of CD needs to be investigated.

012 ASSOCIATION OF MULTIDRUG RESISTANCE GENE (MDR1) C3435T POLYMORPHISM WITH EXTENSIVE AND SEVERE ULCERATIVE COLITIS (UC)

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Background and Aims: The MDR1 gene encodes a transmembrane efflux pump which is highly expressed on intestinal epithelial cells. The UC like phenotype in *mdr1a*-deficient mice and the position of the gene within chromosome 7q22 (putative susceptibility locus), together with recent genetic studies implicate this as a strong IBD candidate gene. The MDR1 SNP C3435T at exon 26 correlates strongly with MDR1 expression (TT allele associated with low expression) and has been shown to be associated with increased susceptibility to UC. We tested whether this SNP is associated with UC and performed further genotype–phenotype analysis in a large well characterised Caucasian cohort.

Methods: Allelic and genotype frequencies of MDR1 C3435T SNP were investigated in 306 patients with UC, 268 with Crohn's disease (CD), and 311 healthy controls using TaqMan assay.

Results: The TT genotype and T-allelic frequencies were significantly higher in patients with UC compared to healthy controls (58.5% *v* 51.3%, p = 0.011, OR 1.34, CI 1.07 to 1.68 and 36.6% *v* 25.4%, p = 0.023, OR −1.68, CI 1.07 to 2.63, respectively). No association was observed with CD. The TT genotype and allele demonstrated stronger association with severe and extensive UC (table 1). No other genotypic–phenotypic correlations were observed with UC and CD.

Conclusion: These data suggest that the MDR1 gene encodes determinants of disease susceptibility and behaviour UC. Further detailed haplotype analysis and functional studies are necessary to establish this.

Abstract 12 Comparisons of T genotype and allelic frequencies in extensive and severe UC with healthy controls

UC phenotype	TT (%)	p Value (OR, 95% CI)	T allele (%)	p Value (OR, 95% CI)
Extensive (n = 116)	43 (37.1)	0.035 (2.40;1.25–4.66)	125 (63.8)	0.002 (1.67;1.20–2.33)
*Severe (n = 82)	38 (46.3)	0.008 (2.09;1.04–3.87)	111 (64.5)	0.002 (1.73;1.22–2.45)

*Severe, defined by need for inpatient therapy fulfilling Truelove and Witts' criteria.

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013 FOOD ELIMINATION DIETS FOR IRRITABLE BOWEL SYNDROME: A DOUBLE BLIND TRIAL BASED ON IGG ANTIBODIES TO FOOD

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Many patients with irritable bowel syndrome (IBS) are convinced they have some form of food allergy or intolerance and have usually tried a dietary approach to their problem. IgE mediated food hypersensitivity (allergy) does not appear to be commonly associated with symptoms of IBS, but little attention has been paid to the potential role of IgG food antibodies in this condition. The aim of this study was to assess the therapeutic potential of dietary elimination, based on the presence of IgG antibodies to foods in patients with IBS.

Methods: A double blind randomised controlled trial was undertaken in which 150 outpatients with IBS (all subtypes) were randomised to receive, for 3 months, a diet excluding all foods to which they had raised IgG antibodies (titre >3:1), or a sham diet excluding the same number of foods but not those to which they were sensitive. IgG food antibodies were detected using an ELISA test (York Test Labs, York, UK). The treatment phase was followed by a 1 month reintroduction period in which patients resumed their normal pre-trial diets. Primary outcome measures were the change in IBS symptom severity and global rating scores. Non-colonic symptomatology, quality of life, and anxiety/depression were secondary outcomes.

Results: The true diet led to a significantly greater reduction in symptoms than the sham diet (difference in mean change = 39; 95% CI: 5.2 to 72.3; p = 0.024), with this effect much greater in those who fully adhered to their diets (98; 52 to 144; p<0.001).The global rating score also showed a significant improvement in patients adhering to the true diet (p = 0.006). All other outcome measures showed a trend towards benefit in the true diet group. Relaxation of the diet led to a greater deterioration of symptoms in patients on the true diet (52; 18 to 86; p = 0.003).

Conclusion: A clinically significant improvement can be achieved in some patients with IBS using an elimination diet based on the presence of IgG antibodies to food. The number needed to treat in patients fully adhering to this antibody based diet is in the range of 2.5–3.

014 ARE PATIENTS WITH COELIAC DISEASE SOCIALLY RESTRICTED BY A GLUTEN FREE DIET?

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Background: For patients with coeliac disease (CD), compliance with a gluten free diet (GFD), when eating outside the home, may be difficult. This may depend on chefs' knowledge of GFD. Eating food not prepared at home may inadvertently expose patients to gluten. A GFD may also cause social restrictions and thus impair quality of life.

Aims: We assessed whether there are differences in the eating habits of CD patients when compared to the general public. In addition, we compared chefs' knowledge with the public's knowledge about CD.

Methods: A questionnaire survey about CD was performed in South Sheffield on CD patients, chefs, and the general public. We also questioned these individuals about peanut allergy (PA), a condition of similar prevalence (1 in 100) but where exposure has more immediate consequences to the individual and commercial establishment.

Results: 319 CD patients (mean age 53.8 years, 65.8% female), 515 members of the public (57.2 years, 33.9% female), and 322 chefs (161 restaurant, 161 take-away) (37.6 years, 15.2% female) were interviewed. Only 168 chefs were qualified. 17.1% and 51.2% of chefs had heard of CD and PA *v* 44.2% and 88.5% of the public (p<0.0001, p<0.0001). 26.1% and 58.4% of restaurant chefs had heard of CD and PA *v* 8.1% and 44.1% of take-away chefs, respectively (p<0.0001, p<0.01). 22.0% and 54.2% of qualified chefs had heard of CD and PA *v* 11.3% and 47.7% of non-qualified chefs, respectively (p = 0.021, p = 0.247). CD patients ate less frequently at a friend's house than the general public (p = 0.003). CD patients ate less frequently from take-away establishments (p<0.0001). However, CD patients ate as frequently in restaurants (p = 0.078).

Conclusions: Chefs know less about CD and PA than the general public. Non-qualified and take-away chefs appear to have particularly

limited knowledge. Patients with CD feel justifiably cautious when eating food not prepared at home, and do so less frequently than the general public. Educating chefs about a GFD may alleviate the social restrictions on CD patients.

015 ANTIBIOTIC PROPHYLAXIS AND PEG INSERTION IN NON-CANCER PATIENTS: A DOUBLE BLIND CONTROLLED TRIAL

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Introduction: BSG guidelines advise antibiotic prophylaxis at insertion of percutaneous endoscopic gastrostomy (PEG) tubes. The evidence for these guidelines was largely based upon data from cancer patients; however, the majority of patients requiring PEG insertion in the UK have benign disease. We therefore did a randomised double blind controlled trial to determine whether antibiotic prophylaxis is beneficial for non-cancer patients requiring PEGs.

Methods: 84 patients were randomised to receive a single dose of 2.2 g co-amoxiclav (2 g cefotaxime if penicillin-allergic) or placebo injection, given in the endoscopy room before PEG insertion. Subjects were then reviewed for up to 7 days and development of PEG infection (using objective scoring and microbiological assays) was recorded along with systemic infection (that is, requirement for systemic antibiotics) or other clinical events. Data were analysed using Fisher's exact test. The mean age of patients was 70.4 years. Indications for PEG were stroke (n = 50), senility (9), Parkinson's disease (6), multiple sclerosis (5), motor neurone disease (3), and others (11).

Results: (1) PEG infection; 72 patients were evaluable (of the remaining 12, 6 died before day 7 and without PEG infection, 5 were given antibiotics for systemic infection before PEG infection, and 1 patient pulled the PEG out). PEG infections rates for placebo group were 15/33 (45%) and for antibiotic group 2/39 (5%) ($p<0.01$). However, no patient required PEG removal. (2) Systemic infection; 83 patients were evaluable. Requirements for systemic antibiotics in the placebo group were 14/41 (34%) and in the antibiotic group 4/42 (10%) ($p<0.01$). (3) Mortality (<7 days); 83 patients were evaluable. Mortality was 6/41 (15%) in the placebo group and 2/42 (5%) in the antibiotic group ($p = 0.1$).

Conclusions: Antibiotic prophylaxis before PEG insertion significantly reduces both localised and systemic infection, and may help reduce early mortality.

016 DIETARY SULPHITE AND DISEASE ACTIVITY IN ULCERATIVE COLITIS PATIENTS

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Background: The cause of ulcerative colitis (UC) is unknown, although the relapsing nature and geographical incidence of the disease implicate environmental factors. Sulphiting agents are widely used food additives. Due to the toxicity of sulphur compounds, intakes of sulphited foods are a possible cause of relapse in UC.

Aims: To determine associations between diet and UC disease activity.

Design: 7 day dietary diaries were completed by 71 UC volunteers. A subset (n = 25) completed a second diary 6 months later. A clinical assessment including sigmoidoscopic examination (scale 1–6)[1] was carried out at the end of each 7 day dietary period. Each food (or food group) consumed was given a Food Sigmoidoscopy Score (FSS) calculated by summing the products of food weight and sigmoidoscopy score for each occurrence of the food and dividing by the total weight of the food contained in all diaries. Foods amounting to <1 kg (total for all diaries) or consumed by <10 people were excluded from this analysis, leaving 92 foods. Foods potentially containing sulphite (n = 12) were defined as those foods for which EU regulations permit sulphite addition.[2]

Results: Plotting the maximum permitted sulphite content of an average 7 day intake (for those consuming that food) of each of the sulphited foods against the food's FSS revealed a significant correlation ($r^2 = 0.79$, $p<0.001$). The ''worst'' performing sulphited foods (position after placing foods in order of FSS) were: bitter (92), white wine (89), red wine (88), lager (84), sausages (82), processed fruit pies (81), and soft drinks (75).

Conclusions: Intakes of sulphited foods were associated with increased disease activity in UC. The dietary analysis method used provides a new tool for establishing relationships between diet and disease and a potentially therapeutic diet for UC.

1. **Baron JH**, Connell AM, Lennard-Jones I. *BMJ* 1964;**1**:89–92.
2. **MAFF**. *Food additives regulations.* HMSO, London, 1995:3187.

017 SAFETY OF PERCUTANEOUS ENDOSCOPIC GASTROSTOMY PLACEMENT BY A TRAINED NURSE PRACTITIONER

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Introduction: Percutaneous endoscopic gastrostomy (PEG) is regarded as the first choice for long term enteral feeding and is traditionally placed by two physicians (endoscopist and assistant). However, PEG insertion is associated with considerable morbidity and mortality. Pre-assessment and PEG insertion by a dedicated nurse practitioner (NP) may reduce these risks. We present data from before and after the appointment of a NP at our hospital.

Methods: The NP is an endoscopy nurse who had observed 50 procedures. She is responsible for preparing the abdominal wall, administering local anaesthetic, incision, passing trocar and cannula, and placing and securing the PEG. A trained observer was present during all cases. Indications for PEG and dates of insertion were recorded prospectively from case note studies of consecutive patients undergoing PEG insertion (n = 66 before and n = 121 after appointment) in an ongoing audit. Complication and mortality rates at 30 days were obtained. Appropriate clinical signs treated with antibiotics defined site infection and aspiration.

Results: Data from these groups were analysed. They were matched for age and sex and indication. Complication rates were lower in the NP group with 14/121 (11.6%) compared with 9/66 (13.6%; p = ns) developing site infections, 2/121 (1.7%) *v* 11/66 (16.7%; $p<0.001$) aspiration pneumonias, and 3/121 (2.5%) *v* 10/66 (15.2%; $p<0.01$) tube displacement. 30 day mortality rate was also reduced: 8/121 (6.6%) *v* 11/66 (16.7%; $p = 0.1$).

Conclusions: Our data confirm the safety of PEG insertion by a dedicated NP. Furthermore, since there is no obvious change in age or indication for PEG it may be that the significant reduction in aspiration and PEG displacement and the trend toward lower mortality rates is due to more appropriate patient selection, through pre-assessment by the NP and the development of a specialist PEG team.

018 A PROSPECTIVE COMPARISON OF MESENTERIC ANGIOGRAPHY WITH WIRELESS CAPSULE ENDOSCOPY IN THE DIAGNOSIS OF OBSCURE GASTROINTESTINAL HAEMORRHAGE

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Background: Wireless capsule endoscopy has been shown to be superior to push enteroscopy in gastroscopy and colonoscopy negative GI bleeding. This is not surprising since wireless capsule endoscopy has the potential to visualise the entire length of the small intestine. However, no prospective comparison between mesenteric angiography and wireless capsule endoscopy has been carried out.

Aim: To compare the clinical efficacy of wireless capsule endoscopy with mesenteric angiography in patients with recent GI haemorrhage and negative upper endoscopy, capsule endoscopy, and colonoscopy.

Patients: 17 consecutive patients (11 men; median age 72 years, range 27–84 years) referred for mesenteric angiography to investigate obscure GI haemorrhage were included in the study. The patients had significant GI haemorrhage with haemodynamic instability and or haemoglobin <10g/l. All had been previously investigated and found to have negative upper endoscopy, push enteroscopy (Olympus SIF Q240), and colonoscopy.

Methods: Wireless capsule endoscopy was performed with the Given® M2A capsule after an overnight fast. Mesenteric angiography was performed by femoral artery puncture to introduce a 7Fr catheter and 3 Fr coaxial catheter. Selective injection of contrast into the inferior and superior mesenteric arteries, coeliac axis, middle colic, hepatic, splenic, and gastroduodenal arteries.

Results: Capsule endoscopy detected the source of haemorrhage in 8 out of 17 patients (47%). In 3 out of 17 patients the capsule endoscopy did not give useful video images as the capsule remained in the stomach (2) or a Zenker's diverticulum till the battery was exhausted. Selective visceral angiography detected the source of haemorrhage in 9 out of 17 patients (53%; p = ns). In 9 patients the capsule endoscopy and mesenteric angiography gave concordant results (53%) and in 5 patients the two methods gave discordant findings (29%). Overall, capsule endoscopy and/or mesenteric angiography detected the source of

haemorrhage in 71% of patients, angiodysplasias accounted for the majority of detected lesions.

Conclusion: In this first prospective comparison of capsule endoscopy with mesenteric angiography in obscure GI haemorrhage (negative upper endoscopy, push enteroscopy, and colonoscopy), both investigations had a comparable rate of detection of the source of haemorrhage. However, the two procedures were complementary and together detected the source of haemorrhage in 71% of patients.

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019 MALIGNANCY AND MORTALITY IN PEOPLE WITH COELIAC DISEASE: A GENERAL POPULATION BASED COHORT STUDY

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Introduction: People with coeliac disease may be at increased risk of gastrointestinal malignancy, lymphoma, and mortality, but at decreased risk of other cancers. We performed a population based cohort study using the General Practice Research Database to quantify the risks in people with coeliac disease compared with the general population.

Methods: We identified 4732 people with coeliac disease and 23620 age and sex matched control subjects. We analysed our data using Cox regression.

Results: Among the people with coeliac disease 134 had at least one malignancy and 237 died. The overall hazard ratios were: for any malignancy 1·29 (95% CI 1·06 to 1·55), for mortality 1·31 (95% CI 1·13 to 1·51), for gastrointestinal cancer 1·85 (95% CI 1·22 to 2·81), for breast cancer 0·35 (95% CI 0·17 to 0·72), for lung 0·34 (95% CI 0·13 to 0·95), and for lymphoproliferative disease 4·8 (95% CI 2·71 to 8·50). Further analysis showed that the increased risk was primarily in the first year after diagnosis, with only the risk for lymphoproliferative disease remaining significantly raised subsequently. After excluding events in the first year following diagnosis the hazard ratio for malignancy was 1·10 (95% CI 0·87 to 1·39) and for mortality 1·17 (95% CI 0·98 to 1·38) giving absolute excess rates of 0·6 and 1·7 per 1000 person years, respectively.

Interpretation: There were modest increases in the overall risks of malignancy and mortality in people with coeliac disease and most of this excess risk was in the first year of follow up after diagnosis. We found a marked reduction in the risk of breast cancer in people with coeliac disease and the mechanism of this merits further attention as it may provide insight into the aetiology of this common malignancy.

020 COELIAC DISEASE: T CELL IMMUNOGENICITY AND IN VIVO TOXICITY OF THE HMW GLUTENINS

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Introduction: Wheat gluten comprises gliadins, which exacerbate coeliac disease (CD), and glutenin subunits, whose role in CD remains obscure. We wished to study T cell immunogenicity and in vivo toxicity of high molecular weight glutenin subunits (HMW-GS).

Methods: HMW-GS (1Dx5, 1Dx7, 1Dy9, 1Dy10) were separated chemically from Rektor wheat flour, and their purity checked by SDS-PAGE, HPLC, and gliadin ELISA. Small intestinal biopsies from CD patients (n=13) were incubated overnight with gluten. T cell lines were cultured and tested after 1 to 5 weeks for their reaction to HMW-GS. 500 mg of HMW-GS were instilled into the duodena of two further patients with known CD, who were taking a gluten-free diet. Biopsies were taken at 0, 2, 4, and 6 h after challenge and assessed for villous height to crypt depth ratio (VH:CD), enterocyte cell height (ECH) and intra-epithelial lymphocyte count (IEL), and stained for interleukin 15 (IL15).

Results: Purified HMW-GS were less than 1% contaminated with other gluten proteins. T cell lines from 8 of 13 patients showed positive stimulation to HMW-GS (stimulation indices from 2 to 12). Both patients challenged in vivo showed significant changes in VH:CD and ECH, maximal at 4 h. IEL rose at each time point with a maximum at 6 hours. Staining of lamina propria cells with IL15 was observed from 2 h.

Discussion: Our results demonstrate the presence of HMW-GS specific T cells in CD small intestine, and the in vivo toxicity of this fraction. The demonstration of IL15 staining at 2 h indicates that HMW-GS might be toxic via early mediators, prior to the activation of antigen specific CD4+T cells. The fraction consists of four different subunits (numbers 5,7,9,10). Our data do not indicate the relative toxicity of single subunits, whose preparative separation by chemical means is difficult. Use of pure recombinant HMW-GS in similar experiments will elucidate the suitability of these proteins for inclusion in foods for consumption by patients with CD.

021 NON-RESPONSIVE COELIAC DISEASE—EXPERIENCE OF A TERTIARY REFERRAL CENTRE

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Background: Failure to respond to a gluten free diet, either clinically or histologically, defines non-responsive coeliac disease. Refractory coeliac disease is rare and describes persisting gluten induced enteropathy when other causes have been excluded. The prognosis is poor and there is a high incidence of enteropathy associated T cell lymphoma. Therefore, all patients with primary or secondary non-responsive coeliac disease should be extensively investigated. We aim to review our retrospective experience of this group.

Patients: We currently have 170 coeliac patients under regular review, with three-quarters of these referred to our department after their diagnosis. We identified those with a history of non-responsive coeliac disease and examined the documented causes in each case, including a dietary assessment. The criteria required to reach a diagnosis was either a positive test result or improvement in duodenal histology and/or symptoms with the appropriate treatment for that condition. Those patients with persistent abnormal duodenal histology, with no other cause after extensive investigation, were assumed to have refractory coeliac disease.

Results: 73 patients did not respond satisfactorily to a gluten free diet. On questioning, 15 (21%) admitted non-compliance and 18 (25%) were found to be inadvertently consuming gluten. Microscopic colitis was diagnosed in 9 (12%) patients and bacterial overgrowth in 5 (7%) individuals who had a positive breath test. A further 9 patients were thought to have predominantly functional symptoms with normal duodenal histology. 11 further relevant diagnoses were made including lactose intolerance, inflammatory bowel disease, immunodeficiency, and colorectal cancer. 8 (12%) patients were assessed as having refractory coeliac disease and, on further investigation, 2 had ulcerative jejunitis and 2 were found to have intestinal lymphoma. Overall 15 patients received oral steroids, 9 were prescribed azathioprine and 2 were given cyclosporin.

Conclusions: Continued gluten ingestion is still the predominant cause of non-response to dietary treatment in coeliac disease. Thorough assessment will identify a potentially treatable cause in the majority of patients.

022 ASSOCIATION OF ADULT COELIAC DISEASE WITH SURGICAL ABDOMINAL PAIN: A CASE CONTROLLED STUDY IN PATIENTS REFERRED TO SECONDARY CARE

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Background: Acute abdominal pain is the most common indication for surgical admission. Within this group of patients, non-specific abdominal pain (NSAP) may account for up to 40% of cases. Although patients with coeliac disease may describe abdominal pain as a significant presenting symptom, there has been no published prospective study in which adult patients with acute abdominal pain (warranting admission) are investigated for coeliac disease. We aimed to assess the association of coeliac disease with surgical abdominal pain.

Methods: A case control study was undertaken at a single university hospital. 300 consecutive new patients admitted with acute abdominal pain and healthy controls (age and sex matched) without abdominal pain were initially investigated for coeliac disease with immunoglobulins, IgA/IgG antigliadin, and endomysial antibodies. Any patient with a positive IgA AGA, EMA, or only IgG AGA in the presence of IgA deficiency was offered a small bowel biopsy to confirm the diagnosis of CD.

Results: There were 33 patients with abdominal pain who had positive antibodies; of these 9 had coeliac disease (6 EMA positive; 3 EMA negative). There was 1 antibody positive patient (EMA in isolation) who declined duodenal biopsy and 23 had normal duodenal mucosa. There were 2 cases of coeliac disease in the control group, of which one was EMA positive. There was a significant association of coeliac disease with abdominal pain compared with controls ($p=0.03$, $\chi^2=4.5$, odds

ratio = 4.6 (95% CI 1.0 to 21.5)). When considering NSAP exclusively the prevalence of coeliac disease was 10.5% (9/86).

Conclusion: When patients with NSAP are referred to secondary care the diagnosis of coeliac disease should be considered. Using only EMA, 3 out of 9 cases would have been missed.

023 PROSPECTIVE STUDY OF THE PREVALENCE OF EXOCRINE PANCREATIC INSUFFICIENCY IN ADULT COELIAC DISEASE USING FAECAL ELASTASE-1 (FEL-1)

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Introduction: Continuing gastrointestinal (GI) symptoms in patients with coeliac disease (CD) may indicate continued gluten exposure. However, a proportion of patients with CD still have GI symptoms, particularly diarrhoea, even with strict adherence to a gluten free diet (GFD). These patients are often assessed for other associated causes. Exocrine pancreatic insufficiency can be assessed using the Fel-1 assay. This has been shown to be highly sensitive and specific particularly for moderate and severe exocrine pancreatic insufficiency. However, Fel-1 has not been evaluated in CD patients.

Aim: To assess the prevalence of exocrine pancreatic insufficiency in patients with CD with particular reference to those with persistent GI symptoms.

Patients and Method: We recruited patients from the specialist coeliac clinic. Patients were assessed for the following factors: 1) duration of CD, 2) compliance to GFD (based on antibody status), and 3) the presence of continued GI symptoms. All patients attending were invited to produce a stool sample that was assayed for Fel-1 using ELISA.

Results: 117 patients were recruited into the study (29 males, median age 52 years) of which 22 patients had a Fel-1<200 (18.8%).

CD patients with persisting GI symptoms were significantly more likely to have exocrine pancreatic insufficiency when compared to the other groups (χ^2 p = 0.02). Compliance to GFD was similar in both groups.

Abstract 23

	n = 117	Fel-1<200	Fel-1>200	%
New CD<6 months)	26	2	24	7.7%
Asymptomatic	51	7	44	13.7%
Ongoing GI symptoms	40	13	27	32.5%

Conclusion: The overall prevalence of exocrine pancreatic insufficiency in CD is 18.8%. In CD patients with persistent GI symptoms Fel-1 is of value for the assessment of exocrine pancreatic insufficiency.

024 ARE LOWER GASTROINTESTINAL INVESTIGATIONS NECESSARY IN PATIENTS WITH COELIAC DISEASE?

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Introduction: Patients with coeliac disease (CD) may present with iron deficiency anaemia (IDA). Previous investigators have suggested that there may be significant dual pathology in patients with IDA. CD patients with persisting diarrhoea (after commencing a gluten-free diet (GFD)) may also require lower gastrointestinal (GI) investigations.

Aim: To assess the value of colonoscopy in patients with CD who present with IDA and CD patients who have persisting diarrhoea.

Abstract 24 Findings at colonoscopy, for different groups

Diagnosis	n	Total with GI pathology (%)	Adenoma (%)	Cancer (%)	IBD (%)	LC (%)
CD & IDA	98	12/98 (12.2)	8 (8.2)	3 (3.1)	0	1 (1)
IDA controls	362	62/362 (17.1)	41 (11.3)	21 (5.8)	0	0
CD & GI symptoms	37	1/37 (2.7)	0	0	0	1 (2.7)
Diarrhoea controls	392	55/392 (14)	16 (6.6)	2 (0.5)	35 (8.9)	2 (0.5)

LC, lymphocytic colitis.

Method: 98 patients with CD (who presented with IDA) and 37 CD patients with persisting diarrhoea were prospectively investigated with colonoscopy (n = 135, age 37–92, median 53). The control group comprised patients referred directly to colonoscopy for investigation of IDA (n = 362, age 22–94, median 64) or diarrhoea (n = 392, age 17–91, median 36).

Results: The colonoscopic yield was not significantly different when comparing CD patients who presented with IDA against the control group ($\chi^2 = 0.24$). However, comparison between CD patients with persisting symptoms and controls was significant ($\chi^2 = 0.05$).

Conclusion: Lower GI investigations are recommended in patients with CD who present with IDA. However, for those patients with CD who have persisting GI symptoms (while on a GFD), a rigid sigmoidoscopy, and rectal biopsy may be the only lower GI test necessary to ensure they do not have LC.

025 ADULT SMALL INTESTINAL TRANSPLANTATION IN ENGLAND AND WALES

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Background: Two transplantation centres in the UK are commissioned by the National Specialist Commissioning Advisory Group for England and Wales to assess small intestinal transplantation in adults. The joint experience of the two centres is presented.

Methods: Patients with irreversible small intestinal failure and complications of parenteral nutrition and those with abdominal disease requiring extensive visceral resection, were assessed as candidates and where appropriate listed for surgery.

Results: 36 patients were assessed for small intestinal transplantation and, of these, 14 underwent surgery. 12 patients survived the transplantation procedure. Of these, 7 patients were alive at one year, 5 at three years, and 3 at five years. Three patients remain alive. Patient and graft survival improved with experience; the survival rates improved for the last half of this experience. One year survival from 43 to 57% and the five year survival from 29 to 43%.

Conclusion: Small intestinal transplantation is associated with a high mortality rate but may benefit carefully selected patients in whom conservative management is likely to carry a greater mortality.

026 MOLECULAR ABNORMALITIES OF SMALL BOWEL ADENOCARCINOMA—APC IS NOT THE CULPRIT

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Background: Primary small bowel adenocarcinoma is rare (1% of all gastrointestinal malignancies). The reason for this is unknown and the mechanisms of carcinogenesis remain unclear. We aimed to investigate the molecular abnormalities in small bowel cancer.

Methods: 100 cases of primary small bowel adenocarcinoma were retrieved from the British Society of Gastroenterology National Survey (June 1998 to May 2000). A review of departmental histopathology records (1980–2002) identified 61 small bowel cancers and 61 pancreatic and 33 ampullary cancers for comparison. All specimens were graded and staged according to the UICC TNM Classification (1997). Tissue microarray technology was employed to allow high throughput immunohistochemistry. Monoclonal antibodies for tumour suppressor genes p53 and SMAD4, mismatch repair genes hMLH-1, hMSH-2, and the APC/β-Catenin/Cyclin D1 pathway were used. Statistical analysis was performed using the χ^2 squared test.

Results: Of the 161 cases of primary small bowel adenocarcinoma collected, 58 were duodenal, 53 jejunal, 46 ileal, and 4 unknown. Positive staining of p53 was present at a significantly higher frequency in the small bowel cancers compared with the pancreatic cancers; duodenum (72%), jejunum (75%), and ileum (70%) *v* pancreas (53%) (p = 0.01). Although negative staining for APC occurred in 10% or less of small bowel cancers, up to 61% showed abnormal staining for β-Catenin and 55% demonstrated overexpression of cyclin D1.

Conclusion: The p53 and APC-β-Catenin pathways play an important role in small bowel carcinogenesis. However, the low incidence of APC loss suggests that APC is not the primary molecular abnormality leading to disruption of the APC- β-Catenin pathway.

027 COELIAC DISEASE AND SMALL BOWEL ADENOCARCINOMA—AN INITIAL ANALYSIS OF THE UNDERLYING MECHANISMS

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Background: Coeliac disease is a chronic sensitivity to gluten, leading to characteristic small intestinal mucosal abnormalities. Malignancy is a recognised complication, although the absolute risk is very small. The mechanisms for neoplastic development are unknown. We aimed to explore the immunohistochemical alterations within celiac associated small bowel cancers compared to non-coeliac cases.

Methods: 161 cases of primary small bowel adenocarcinoma were identified from: The British Society of Gastroenterology National Survey (June 1998 to May 2000, 100 cases) and histopathology records within the Leeds Teaching Hospitals Trust (1980–2002, 61 cases). Seventeen (11%) cases were associated with coeliac disease. All specimens were graded and staged according to the UICC TNM Classification (1997). Use of tissue microarray technology evaluated immunohistochemical differences between celiac associated small bowel cancers and non-coeliac cases. Monoclonal antibodies for tumour suppressor genes p53 and SMAD4, mismatch repair genes hMLH-1, hMSH-2, and the APC/β-Catenin/Cyclin D1 pathway were used. Statistical analysis was performed using the χ^2 squared test.

Results: Of the 161 cases of primary small bowel adenocarcinoma, 58 were duodenal, 53 jejunal, 46 ileal, and 4 unknown. Coeliac associated cancers were distributed as 8 duodenal, 7 jejunal, and 2 ileal. In 6 cases coeliac disease was diagnosed at the time of presentation of the small bowel cancer. Eleven patients had been treated with a gluten free diet for between 1 and 24 years. β-Catenin expression was abnormal in 14 of 16 cases of celiac associated small bowel adenocarcinoma compared with 62 out of 133 of non-coeliac cancers ($p<0.002$). Immunohistochemical analysis of all other antibodies revealed no significant difference between the two groups.

Conclusion: β-Catenin expression is abnormal in the majority of celiac associated small bowel adenocarcinomas. This suggests that β-Catenin may play an important role in the development of these cancers.

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028 QUALITY OF PERFORMANCE AT SCREENING FLEXIBLE SIGMOIDOSCOPY CORRELATES WITH ADENOMA DETECTION RATES

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Background: Adenoma detection rates (ADR) at screening flexible sigmoidoscopy (FS) are known to be variable. We have previously described an objective performance score for screening FS based on video footage.

Aims: To determine whether quality of exam performance correlates with ADR.

Methods: Video footage from 260 FS cases was selected from 40000 cases from the UK Flexible Sigmoidoscopy Screening Trial. The endoscopic view of the extubation phase of 20 cases from each of the 13 endoscopists were edited together in batches of 5 (4 batches per endoscopist), and then randomised. Each batch of 5 was from the same endoscopist. Cases in each batch had the same grade of bowel preparation; excellent, good, adequate, or a mixture of these grades. Each endoscopist had cases with all grades of prep. An experienced scorer, blinded to the endoscopist's identity, gave a single ''quality of performance'' score for each batch of five cases; scores given were from 5–1 where 5/4 = excellent/good, 2/1 = not good enough/unacceptable.

Results: Total scores for endoscopist performance ranged from 9–17 (maximum possible 20) and the mean batch score for each endoscopist ranged from 2.25–4.25. The endoscopists fell into two groups. Six of the 13 with a mean batch score >3 had a higher ADR of 12.6–15.9%. Seven of the 13 with a mean batch score $\leqslant 3$ had a lower ADR of 8.6–11.8%; 5 of these had a score of <3, defined as being not good enough or unacceptable. ADR was strongly correlated with the total performance score: Pearson correlation coefficient 0.79 ($p=0.001$).

Conclusions: An endoscopist's performance at screening flexible sigmoidoscopy can be judged using video footage. Good performance correlates with higher adenoma detection rates. This tool could be used to improve technique and ensure quality in screening flexible sigmoidoscopy.

029 THE ROLE OF FOLLOW UP ENDOSCOPY (OGD) FOR GASTRIC ULCERS

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Introduction: Several studies have demonstrated that without endoscopic or histological suspicion of malignancy, follow up OGD of gastric ulcers is unnecessary. Despite this, recent BSG guidelines[1] recommend universal follow up OGD for these patients. In High Wycombe we have for some years followed an informal policy of not following up if the endoscopist is confident that GUs are non-malignant. In view of the guidelines we reviewed our practice.

Methods: We collected histopathology details of all gastric carcinomas diagnosed between 1/3/1997 and 29/7/2002. From our endoscopy reporting system we got data on all OGDs carried out between these dates. We examined the notes of patients with a diagnosis of gastric carcinoma to ascertain whether endoscopic follow up had been carried out, and if not whether having carried it out might have speeded up diagnosis. In addition we were able to examine the total number of gastric ulcers diagnosed and the number of OGDs carried out specifically to follow them up.

Results: 9586 OGDs were performed over the study period and 368 unique patients were diagnosed with gastric ulcer. Of these 158 had an OGD to check for ulcer healing, and in total 194 OGDs to check ulcer healing were performed. 72 gastric carcinomas were histologically diagnosed (62 via OGD, 9 via postmortem, and 1 at surgery). 49 of 62 had a carcinoma diagnosed at the index endoscopy. Of the other 13, 6 were suspected on endoscopic appearances and confirmed at repeat OGD. Of the other 7 only 3 were not endoscopically followed up and none of these had an ulcer. A further 2 had the ulcer obscured by bleeding. The last 2 cases were one in which the ulcer healed fully but malignancy was diagnosed at a remote site in the stomach later and one in which biopsies of a healing ulcer and it's scar were benign (malignancy later developed involving stomach and ovary, the primary remains unclear).

Discussion: Over the past five years we have endoscopically and histologically followed up under half of gastric ulcers. 49 of 62 gastric carcinomas were diagnosed at the first OGD, only 2 with a fully visible ulcer were not suspected at the first OGD, and neither of these would have been detected earlier following the current guidelines. Endoscopic follow up of gastric ulcers is not always necessary and would have necessitated over 200 extra endoscopies for our patients without any clear benefit.

1. Dyspepsia Management Guidelines. BSG, 2002.

030 THE ROLE OF HIGH MAGNIFICATION CHROMOSCOPIC COLONOSCOPY IN HNPCC CANCER SCREENING

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Background: HNPCC is the most common of the hereditary colon cancer syndromes approximating to 1.5% of the colon cancer (CC) burden in the UK. HNPCC is associated with right sided CC. In addition to exophytic polyps, flat and depressed lesions occur which undergo an accelerated adenoma-carcinoma sequence in addition to *de novo* neoplastic transformation. Such lesions are difficult to detect using conventional colonoscopy.

Aim: To evaluate the efficacy of high-magnification-chromoscopic colonoscopy (HMCC) for the detection of neoplastic lesions in patients with HNPCC.

Methods: Consecutive asymptomatic patients fulfilling modified Amsterdam criteria underwent a two stage colonoscopy of the right colon using the Olympus CF240Z. Following caecal intubation, the right colon was examined using conventional colonoscopy then re-intubated and examined again using high-magnification pan-mucosal chromoscopy. Identified lesions at each stage were classified according to the Japanese Research Society (JRSC) guidelines. Diagnostic extubation time was fixed at 10 mins.

Results: 18 patients (12 hMSH2/hMLH1 germline mutation positive). Caecal intuabtion 18/18 (100%), 11 male (61%), mean age 44 years (range 23–54 years). 53 lesions were identified in 12 patients.

Abstract 30

Conventional colonoscopy	Lesion characteristics JRSC	n	Median size (mm)	Histology HP	Adenoma (LGD)	Adenoma (HGD)	IN	n
	Ip/Isp	16	8 (4–12)	7	6	3	0	16
	II	4	6 (3–8)	0	2	1	1	4
Total				7	8	4	1	20
HMCC	Ip/Isp	17	8 (4–12)	7	7	3	0	17
	II	16	3 (1–6)	2	10	4	0	16
Total				9	17	7	0	33
Combined total				16	25	11	1	53

HD, hyperplastic; IN, invasive neoplasia.

Conclusions: HMCC improves the detection of flat neoplastic lesions in HNPCC. Endoscopic screening in this ''high risk'' group may be enhanced using HMCC.

Significantly more flat lesions were detected using HMCC *v* conventional colonoscopy ($p<0.01$). Of the 6 flat lesions with HGD or beyond, 4 (67%) would not have been detected using conventional colonoscopy.

Conclusions: HMCC improves the detection of flat neoplastic lesions in HNPCC. Endoscopic screening in this high risk group may be enhanced using HMCC.

031 RECTAL ABERRANT CRYPT FOCI IDENTIFIED USING HIGH-MAGNIFICATION-CHROMOSCOPIC COLONOSCOPY: BIOMARKERS FOR RIGHT-HEMI-COLONIC FLAT AND DEPRESSED NEOPLASIA

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Background: Aberrant crypt foci (ACF) may represent pre-neoplastic lesions in the human colon. The prevalence of ACF detected using magnification chromoscopic colonoscopy is known to follow a stepwise progression from normal subjects to those with exophytic adenomas and colon cancer (CC). No studies have addressed the prevalence of rectal ACF in patients with flat and depressed colonic lesions that cluster within the right hemi-colon and may undergo *de novo* neoplastic transformation.

Methods: All patients underwent total colonoscopy by a single endoscopist using the Olympus CF240Z magnifying colonoscope. Prior to extubation, pan high-magnification-chromoscopy using indigo carmine was applied to the rectum and the distal 10 cm of mucosa examined using forward and retroflexed views. ACF were defined as two or more crypts with dilated or slit-like openings that were raised above the adjacent mucosa. Univariate logistic regression was used to assess the ability of the number of ACF to discriminate between 3 groups (normal, adenoma, cancer).

Abstract 31

	n	Total no. ACF	Median no. ACF	% ACF	% dysplastic ACF
Endoscopically normal	574	602	1 (0–5)	15	3
JRSC II adenoma (LGD+HGD)	281	2796	9 (1–22)	82	18
JRSC II cancer (T2 or beyond)	14	594	38 (14–64)	100	61

Results: n = 1000, mean age 53 years (range 18–98), male 561 (56%), caecal intubation 958 (96%). Logistic regression: endoscopically normal *v* JRSC II adenoma $p<0.01$. JRSC type II adenoma *v* JRSC type II cancer $p<0.001$.

Conclusions: The number of ACF in normal patients, patients with JRSC II adenoma, and JRSC II cancer follow a stepwise incremental change as previously observed for exophytic adenomas and cancer. Detection of ACF in the rectum may be a useful biomarker for proximal colonic flat neoplasia and could be used at index flexible sigmoidoscopic screening to stratify risk of right-hemi-colonic neoplasia. Patients with dysplastic ACF of high density should receive total colonoscopy.

032 ENDOSCOPIC MUCOSAL RESECTION FOR LATERAL SPREADING TUMOURS OF THE COLORECTUM: A PROSPECTIVE ANALYSIS

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Background: Lateral spreading tumours (LSTs) are superficial spreading neoplasms now increasingly diagnosed using chromoscopy. The clinicopathological features and safety of EMR for LSTs (G-type ''aggregate'' and F-type ''flat'') has yet to be clarified in Western cohorts.

Abstract 32

Endoscopic class	Histology Adenoma	Carcinoma in situ	sm3 invasive carcinoma	Anatomical location right colon	left colon
G-type n = 42	18	21	3	18 (43%)	24 (57%)
F-type n = 23	2	13	8	17 (74%)	6 (26%)

Methods: Patients underwent magnification-chromoscopic-colonoscopy using the Olympus CF240Z by a single endoscopist. All lesions were examined initially using indigo carmine chromoscopy to delineate contour followed by crystal violet for crypt analysis. Exclusion criteria for EMR were: 1) lesions with a Kudo type V(n) crypt or high frequency (20Mhz) mini-probe ultrasound confirmed T2 disease; 2) spread over two consecutive folds; and 3) asymmetrical lift at submucosal injection. These lesions were cold biopsied only and referred for surgery. EMR (piecemeal or *en block*) was used for eligible lesions. Anatomical location of lesions and complications were recorded.

Results: 65 lesions were diagnosed in 62 patients, 23 F-type and 42 G-type (mean+/-SD 45.5 (SD12) mm and 24 (SD 8.5) mm, respectively)($p<0.01$). 14 underwent surgical resection (9 staged T2 or beyond endoscopically, 3 due to failed endoscopic resection, 2 due to non-lifting). 51 patients completed EMR. Bleeding occurred in 3 (5%) patients (2 immediate, 1 delayed requiring transfusion) with 1 caecal perforation (clip repaired).

F-type LSTs were more commonly found in the right colon as compared to G-type ($p=0.02$) and were more often associated with sm3 invasion ($p<0.03$). Local recurrence was diagnosed in 3 (6%) at a median follow up interval of 6 months (range 3–18 months).

Conclusions: This study is the largest prospective analysis of LSTs within the west. F-type lesions have a higher malignant potential than G-type and have a propensity for the right colon. G-type LSTs show low rates of sm3 invasion. EMR is a safe and effective therapy for LSTs despite their large size.

033 OPTICAL BIOPSY OF COLONIC LESIONS: COMPARISON OF ELASTIC SCATTERING SPECTROSCOPY WITH HISTOLOGY

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Introduction: Diagnosis of colonic pathology requires conventional histology of multiple biopsies, which has a high sampling error and a low diagnostic yield. Elastic Scattering Spectroscopy (ESS) is a novel optical technique, which can distinguish between normal and abnormal tissue instantaneously in vivo. We present our initial results using this novel technology in the colon.

Aims and Methods: The study compared ESS with conventional histology for differentiating normal colonic mucosa from colonic polyps, colitis, and cancer. Elastic scattering spectra were obtained from 138 sites in 45 patients at colonoscopy. Matched biopsies were taken for histology. Spectral acquisition took less than 1 s. Histologically, the biopsies were defined as normal, hyperplastic polyps, chronic ulcerative colitis, adenomas with dysplasia or carcinoma. Results were analysed using linear discriminant analysis with cross validation.

Results: 483 spectra were analysed (290 normal colonic spectra; 19 hyperplastic polyp spectra from 4 polyps; 69 adenomatous polyp spectra from 23 polyps; 74 chronic colitis spectra from 17 sites; 31 colorectal cancer spectra from 12 sites). The sensitivity and specificity of differentiating hyperplastic polyps *v* adenomas was 84% and 84% respectively; for adenomatous polyps *v* cancer, 80% and 75%, respectively; for normal *v* colitis 77% and 82%, respectively; and for colitis *v* dysplastic mucosa from polyps they were 85% and 88%, respectively.

Conclusion: Despite small data sets particularly for hyperplastic polyps, these data suggest that ESS may be capable of differentiating various colonic lesions in real time allowing an in vivo optical biopsy measurement. It may be valuable in targeting polypectomy and dysplasia surveillance in patients with chronic UC.

034 INFORMED CONSENT: MISSION IMPOSSIBLE

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Aims: Over the past two years we have developed a nurse led information service and shown that it improves patients' satisfaction and perceived understanding of ERCP. To validate this consent process we investigated patients' true understanding of the procedure they were to undergo and the correlation with patients' perceived level of understanding.

Methods: Over a 10 week period patients attending for ERCP were asked to be assessed. After information about the procedure had been given and consent obtained by the specialist radiology nurses patients were interviewed and a mini-mental test (MMT) performed. They were asked to fill in a multiple choice questionnaire (MCQ) regarding their procedure based on written information received from the nurses. Visual analogue scores were recorded of patient satisfaction, understanding, and anxiety before and after filling in the questionnaire.

Results: 48 patients could be included. The median MMT score was 9 (1–10). The mean correct MCQ mark was 55% (5–95%). Poor marks correlated significantly with increasing age and a reduced MMT score. Perceived understanding of the procedure dropped from a median of 85% (0–100%) to 81% (0–100%) after answering the MCQ. No correlation between perceived and actual understanding existed prior to the MCQ, but these were significantly linked after the test. 95% of patients rated the MCQ as useful. Patients' anxiety was unrelated to the level of understanding.

Discussion: Although patients on the whole believe they understand explanations given to them, in reality they know disappointingly little. This questions the validity of ''informed'' consent and needs to be taken into account when talking to patients. A short ''exam'' prior to the procedure increases the actual understanding and improves consent.

035 DOES ENDOSCOPY ALTER MANAGEMENT FOR SIMPLE REFLUX DISEASE

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Background: The role of endoscopy for patients with simple gastro-oesophageal reflux disease is unclear particularly under the age of 55 years. We report the influence of endoscopy on the management of 100 patients with uncomplicated reflux symptoms.

Methods: One hundred consecutive patients undergoing diagnostic upper gastrointestinal endoscopy solely for uncomplicated reflux symptoms were identified using a prospective endoscopy database. Endoscopy results letters were reviewed and, if necessary, the clinical notes were used to identify anti-secretory therapy prior to and after endoscopy. Age, other pathology, and post-procedure instructions were assessed. The cost of anti-secretory therapy was calculated for therapy prior to endoscopy and for the recommended medication after.

Results: Median age was 52 years, 56% of patients were under the age of 55. Only nine percent had no change in management. Anti-secretory therapy was reduced in 41% (1 stopped, 2 changed to lower dose proton pump inhibitor (PPI), and 38 were changed to ''on-demand'' PPI). Therapy was increased in the other 50% (2 on ranitidine, 2 on on-demand PPI, 30 on PPI, and 16 on long term PPI). For 9 patients this increase was for other reasons (gastroduodenal ulceration in 3, duodenitis in 3, and aspirin in 3). Columnar epithelium was identified in 9% and Barrett's oesophagus was confirmed in 5%. Patients under 55 years had anti-secretory therapy increased in 43% and reduced in 52%. Over 55 years, 59% had their therapy increased and 27% had it reduced. For the under 55 age group there was a saving in the cost of prescribed drugs of £175 per patient in the first 2 years, £267 over 3 years, and £359 over 4 years. Endoscopy at our unit costs £290 and after 3¼ years this is equalled by the savings from reduction in prescribing.

Conclusion: Endoscopy for simple reflux symptoms led to a change in management in 91% of cases. For patients under the age of 55 more than half had a reduction in the use of PPI therapy following endoscopy and this could lead to substantial financial savings. We conclude that endoscopy changes management in simple reflux disease and that it may be cost effective in younger patients.

036 ENDOSCOPIC GASTROPLICATION FOR THE TREATMENT OF PAEDIATRIC GASTRO-OESOPHAGEAL REFLUX DISEASE: 12 MONTH FOLLOW UP RESULTS

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The aim of this work is to assess the medium term efficacy of the BARD Endocinch© device for the treatment of GORD in children and adolescents. 17 (5 male) consecutive children, age 12.4 years (6.1–15.9), weight 46.0 kg (16.5–87.5) with symptoms of GORD dependent on PPIs for>12 months or refractory to PPIs underwent endoscopic gastroplication (EG), and follow up occurred for a median of 15 months. Symptom scoring, upper GI endoscopy, oesophageal manometry (in 4), gastric scintiscan, 24 hour oesophageal pH, and completed reflux quality of life (QOLRAD) were at 0, 6 and 52 weeks. Repeat 24 hour pH was performed at 2 (n = 17) and 12 (n = 9) months. Median duration of the procedure for 3 placations was 65 minutes. Improvement in heartburn ($p = 0.001$), regurgitation ($p = 0.002$,), and nausea score (frequency x severity) ($p = 0.013$) was sustained at 12 months. Total, and all sub-parameters, of QOLRAD showed sustained improvement. Total QOLRAD (max 175) increased from median 101 (range 71–149) to165.6 (range 106.6–175) ($p<0.0002$) at 6 weeks follow up, and 153 (range 111–175) ($p = 0.001$) 12 months. All pH parameters improved significantly. Median reflux index from 16.65% (0.9–67.9%) to 2.5% (0.7–15.7%) ($p = 0.001$) at 6 weeks, and 4.3% (2.2–20.6) ($p = 0.02$) at 12 months. DeMeester scores from 73 (6.1–258) to 11.95 (2.6–59.9) (normal<14.72) ($p = 0.002$) at 6 weeks, and 19.2 (11–41.4) ($p = 0.018$) at 12 months. 14/17 did not require any further PPI use at any stage. One patient had localised gastric bleeding requiring red cell transfusion. This is the first study reporting paediatric experience with an endoscopic anti-reflux procedure and demonstrates medium term sustained efficacy in managing GORD in children.

037 OUTCOME OF ACUTE NON-VARICEAL UPPER GASTROINTESTINAL (GI) BLEEDING IN RELATION TO THE TIME OF ENDOSCOPY AND THE EXPERIENCE OF THE OPERATOR: A TWO YEAR SURVEY

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Background and Aim: Acute upper GI bleeding is a common cause of hospitalisation requiring urgent endoscopy. Several clinical and endoscopic score systems have been used to risk stratify patients and predict outcome, but time of endoscopy and operator's experience have received so far little attention as possible variables. We therefore aimed to assess prospectively the impact of endoscopy timing and staff experience on outcome of non-variceal upper GI bleeders in a large tertiary referral centre.

Material and Methods: All patients admitted to our hospital for acute non-variceal upper GI bleeding over a two year period were potentially eligible for this study. They were managed by a team of 7 endoscopists, on call 24 hours a day, whose experience was categorised into 3 levels; endoscopic treatment was standardised according to Forrest classification of lesions as well as was the subsequent medical therapy (iv PPIs). Time of endoscopy was subdivided in two time periods: 8am–4pm and 4pm–8am. For each category of experience and time periods we compared rebleeding rate, transfusion requirement, need for surgery,

length of hospital stay, and mortality. Multivariate analysis was used to discriminate among the impact of different variables on outcomes.

Results: Study population consisted of 272 patients (mean age 67.3 years) with endoscopic stigmata of haemorrhage. They were equally distributed in the three endoscopists' categories, whereas only 19% of procedures were done out of working hours. Rockall score and Forrest classification at admission did not differ between time periods and endoscopists' categories. At univariate analysis, higher operator's experience was associated with significant reduction in rebleeding rate (14% *v* 37%), trasfusion requirements (1.8 (SD 0.6) *v* 3.0 (SD 1.7) units) as well as surgery (4% *v* 10%), but not length of hospital stay nor mortality. By contrast, outcomes did not significantly differ between the two time periods of endoscopy. On multivariate analysis, Rockall score, Forrest classification and endoscopist's experience were independently associated with rebleeding rate, transfusion requirements, and need for surgery.

Discussion: Endoscopist's experience is an important prognostic factor for acute non-variceal upper GI bleeding. Urgent endoscopy should be therefore undertaken only by highly experienced operators as less expert staff tend to underestimate some risk lesions with a negative influence on haemostasis.

038 ENDOSCOPY POLICY AND RISK OF MISSING UPPER GASTROINTESTINAL (GI) MALIGNANCY IN PATIENTS AGED OVER 55 YEARS—DATA FROM THE SCOTTISH AUDIT OF GASTRIC AND OESOPHAGEAL CANCER (SAGOC)

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Introduction: The British Society of Gastroenterology dyspepsia guidelines suggest that patients with new onset of uncomplicated dyspepsia over the age of 55 years should undergo an urgent endoscopy to exclude upper GI malignancy. However, these guidelines are at variance with those produced by the Scottish Intercollegiate Guidelines Network (SIGN), which advise an *H pylori* test and treat strategy as initial management. What would be the risk of missing upper GI malignancy in patients aged over 55 years if urgent endoscopy was reserved for patients with alarm symptoms only?

Aim: To determine the proportion of patients aged over 55 years with upper GI malignancy who present without alarm symptoms.

Methods: The Scottish Audit of Gastric and Oesophageal Cancer collected data prospectively for all upper GI malignancies diagnosed in Scotland between July 1997 and July 1999. We reviewed the data for all patients over the age of 55 years presenting without ''alarm'' symptoms. These were defined as dysphagia, odynophagia, weight loss, GI bleeding, anaemia, vomiting, history of gastric surgery, and history of peptic ulcer disease.

Results: Of the 3293 patients diagnosed with upper GI malignancy during the 2 year period of the audit, 3003 (91%) were aged over 55 years. Of these, 206 (6.9%) presented without alarm symptoms. However, only 74 of these patients underwent potentially curative surgery and only 50 survived more than 1 year. These figures represent 2.5%, and 1.7%, respectively, of all the patients with upper GI malignancy >55 years age.

Conclusion: A small proportion of the patients with upper GI malignancy >55 years age may have their diagnosis delayed if urgent endoscopy was restricted to patients with alarm symptoms only. However, only a minority of these patients have potentially curable disease.

039 DIAGNOSIS OF TUBERCULOSIS BY ENDOSCOPIC ULTRASOUND GUIDED FINE NEEDLE ASPIRATION

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Aims: Standard diagnostic methods may sometimes fail to achieve a bacteriological diagnosis in patients with tuberculosis (TB). Linear endoscopic ultrasound (EUS) is a sensitive technique for the detection of mediastinal lymphadenopathy, offering the additional possibility of guided fine needle aspiration (EUS-FNA) for cytology and bacteriology.

Patients and Methods: 15 patients (8 male, 7 female, mean age 45 years, range 29–72 years) with a suspected diagnosis of TB were examined. All patients had extensive prior negative investigations including bronchoscopy and broncho-alveolar lavage. Enlarged mediastinal nodes were seen on computed tomography in all cases. EUS and guided FNA was carried out using a curved linear array ultrasound transducer and 22 Gauge Wilson Cook needles used to obtain cytological specimens.

Results: All 15 patients had enlarged mediastinal lymph nodes at EUS (mean size 1.8 cm) located subcarinally (9), in the aorto-pulmonary window (5), or posterior lower mediastinum (1). EUS-FNA provided adequate samples in all cases. Cytology revealed epithelioid granulomata on a dirty background suggestive of tuberculosis in seven patients, sarcoidosis in six, non-Hodgkin's lymphoma in one, and nodular sclerosing Hodgkin's lymphoma in one patient. Mycobacterial cultures were positive in five out of seven patients. Patients with TB and lymphoma were treated accordingly, while those with sarcoidosis were only treated if clinically indicated. No complications related to EUS-FNA occurred.

Conclusions: EUS-FNA of mediastinal lymphadenopathy in patients with suspected TB revealed a variety of diagnoses but was also able to identify patients with a diagnosis of TB. Patients investigated by EUS did not require mediastinoscopy and had no procedure related complications. Trans-oesophageal EUS/FNA is a safe and sensitive technique and is a useful alternative in the diagnosis of tuberculosis, when other non-invasive methods fail.

Liver free papers 040–051

040 ATYPICAL HAEMOCHROMATOSIS ASSOCIATED WITH NOVEL MUTATIONS IN THE FERROPORTIN GENE

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The genetic basis of non-HFE haemochromatosis is being unravelled. Mutations in the ferroportin gene, which encodes a cellular iron-export protein, account for the dominantly inherited HFE4 variant characterised by high ferritin, low transferrin saturation, early Kupffer cell iron loading, and poor venesection tolerance. We describe two novel ferroportin mutations in three cases of non-HFE haemochromatosis with HFE4 phenotype. Ferroportin gene analysis was performed by fluorescent dye terminator PCR cycle sequencing with capillary electrophoresis.

Case 1 is a 48 year old man found incidentally to have a serum ferritin of 3000 μg/l and transferrin saturation 21% with no evidence of cataracts. Liver biopsy showed heavy iron deposition in Kupffer and sinusoidal-lining cells with mild deposition in hepatocytes. Bone marrow trephine showed haemosiderin laden macrophages. He is heterozygous for the novel missense mutation W158C in exon 5 of the ferroportin gene, a known ''hotspot''. Two siblings tested thus far are wild type. Case 2 is a 66 year old woman from a large pedigree suggestive of autosomal–dominant haemochromatosis. She had a persistently raised ferritin of 800 μg/l and severe arthropathy affecting hips and small hand joints. Liver biopsy showed low grade iron deposition in Kupffer cells and hepatocytes. She became anaemic early during her venesection treatment. Her 30 year old son (case 3) was found on family screening at age 22 to have a ferritin of 600 μg/l. His ferritin was later elevated at 1700 μg/l and he has subsequently had 18 venesections. Both patients are heterozygous for the novel ferroportin mutation R489E (exon 8). Other family members are being examined.

Ferroportin gene sequencing should be carried out in all patients with suspected haeomchromatosis and the HFE4 phenotype. Subsequent family screening can detect susceptible individuals; venesection treatment should be embarked on cautiously.

041 CCL25 (TECK) MEDIATES RECRUITMENT OF CCR9^{HIGH} GUT HOMING LYMPHOCYTES TO HEPATIC ENDOTHELIUM IN PRIMARY SCLEROSING CHOLANGITIS

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Introduction: Because the gut and liver share a blood supply and are exposed to gut derived antigens we hypothesised that T cells might undergo an enterohepatic recirculation. If so, this could explain the strong association between inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC). We have previously shown that

Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1), which is usually restricted to gut endothelium, is also expressed by hepatic portal endothelium in PSC, and is capable of supporting a4b7 mediated lymphocyte adhesion. Here we demonstrate expression of the gut associated chemokine CCL25 (TECK) on hepatic sinusoidal endothelium. We also describe the presence of a significant population of $CCR9^{high}$ mucosal lymphocytes (capable of binding CCL25) infiltrating PSC liver tissue, thus supporting our hypothesis.

Methods: CCL25 expression was studied by immunochemistry on fresh explanted liver tissue from patients with PSC. Normal liver, alcoholic hepatitis, autoimmune hepatitis (AIH), and primary biliary cirrhosis (PBC) tissue were used as controls. CCR9 expression on liver infiltrating lymphocytes and matched peripheral blood lymphocytes was assessed by flow cytometry. Furthermore, we assessed the functional nature of $CCR9^{+}$liver infiltrating lymphocytes by performing in vitro chemotaxis assays using recombinant CCL25 (TECK). We also assessed the ability of CCL25 to activate the adhesion of $a4b7^{+}$liver infiltrating lymphocytes to recombinant human MAdCAM-1 in a static adhesion assay.

Results: Flow cytometry of liver infiltrating lymphocytes from patients with PSC revealed the presence of a significant population of $CCR9^{high}$ $CD8^{+}$T-cells compared to controls and matched peripheral blood. CCL25 (the ligand for CCR9) expression was detectable on PSC hepatic sinusoidal endothelium and absent from sinusoidal endothelium in other chronic inflammatory liver diseases (AIH and PBC). We also confirmed that PSC liver infiltrating lymphocytes migrated towards CCL25 in a chemotaxis assay and that CCL25 triggered strong adhesion of lymphocytes to immobilised MAdCAM-1 in a static adhesion assay.

Conclusion: We suggest that a population of $CCR9^{high}$, $a4b7^{+}$gut homing lymphocytes can be recruited to the liver in PSC in response to hepatic expression of MAdCAM-1 and CCL25.

042 BREAKDOWN OF T-CELL TOLERANCE TO THE PRIMARY BILIARY CIRRHOSIS (PBC) AUTOANTIGEN PYRUVATE DEHYDROGENASE COMPLEX IS A B-CELL DRIVEN PROCESS

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The autoimmune liver disease PBC is characterised by autoantibodies reactive with the pyruvate dehydrogenase complex (PDC). Observations from both human and murine settings suggest, however, that the key effecter immune response directed at the target biliary epithelial cells is T-cell, as opposed to antibody, mediated. Two key questions therefore arise. The first is how does T-cell tolerance breakdown to as highly conserved a self-antigen as PDC. The second is what role, if any, does the anti-PDC antibody response play in disease pathogenesis?

We have previously demonstrated that, in a murine model, SJL/J mice are normally fully tolerant immunologically of mouse PDC (mPDC). When exposed to cross reactive bovine PDC (bPDC) they rapidly mount an antibody response cross reactive with mPDC. No breakdown of T-cell tolerance to mPDC is, however, seen. Animals co-sensitised with mPDC and bPDC show, in contrast, breakdown of both T-cell and B-cell tolerance to mPDC. This led us to hypothesise that activated B-cells primed to bPDC are able to present mPDC-derived autoepitopes, thereby priming autoreactive T-cell responses. We utilised a B-cell adoptive transfer model to test this hypothesis. Animals were primed with bPDC, and splenic B-cells isolated by immunomagnetic separation (purity >95%). B-cells from bPDC and control antigen primed animals were adoptively transferred into naïve recipients in the presence or absence of mPDC. 7/9 (78%) animals receiving B-cells from bPDC sensitised animals in the presence of mPDC demonstrated a breakdown of CD4+T-cell tolerance to mPDC. These responses were absent from animals receiving mPDC or primed B-cells alone, animals receiving mPDC with B-cells from an irrelevantly sensitised donor and animals receiving specific B-cells in the presence of an irrelevant antigen.

Conclusion: B-cells primed to foreign antigen but cross reactive with self drive the breakdown of T-cell tolerance to self-PDC seen in PBC.

043 A SIGNIFICANT PROPORTION OF MYOFIBROBLASTS ARE OF BONE MARROW ORIGIN IN HUMAN LIVER FIBROSIS

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Background and Aims: Myofibroblasts of bone marrow origin have recently been found in a number of parenchymal organs such as the gut and kidney. Here we sought to analyse the origin of myofibroblasts within fibrotic liver in two scenarios: 8 male patients (hepatitis B, hepatitis B and D, Wilson's disease, Hepatitis C, B and D, and 4 hepatitis C) who received liver transplants from female donors and subsequently developed liver fibrosis and a female recipient of a male bone marrow transplant who later developed hepatitis C induced cirrhosis.

Methods: Through the use of in situ hybridisation for the Y chromosome we have tracked male cells of extrahepatic origin. The phenotype of these male cells was examined by immunohistochemistry using a panel of antibodies against alpha-smooth muscle actin (α-SMA), vimentin, fibulin-2, and leukocyte common antigen (CD45). Confocal microscopy was performed to confirm the location of the Y chromosome probe within the myofibroblasts nuclei.

Results: We have detected significant numbers of Y chromosome positive cells in fibrotic areas, these cells were found to be positive for α-SMA, vimentin, and fibulin-2 and negative for CD45; thus these Y chromosome positive cells have the phenotype of myofibroblasts. In the liver transplant cases 11.5–22.2% of α-SMA positive myofibroblasts contained the Y chromosome. In the female recipient of the male bone marrow transplant 12.5% of the myofibroblasts were Y chromosome positive indicating a bone marrow origin.

Conclusions: There is a significant contribution to liver cirrhosis in humans from extrahepatically derived myofibroblasts in liver disease of diverse aetiology.

044 THE CONTRIBUTION OF THE BONE MARROW TO LIVER REGENERATION DEPENDS UPON ENDOGENOUS HEPATOCYTE REPLICATION POTENTIAL

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Introduction: Bone marrow cells (BMCs) can contribute to regeneration of the chronically damaged liver, but in human studies and animal models the magnitude of this axis is highly variable. In a murine model of hepatitis B we examined whether this pathway of regeneration is enhanced by inhibiting endogenous hepatocyte regeneration.

Methods: 2 month old female mice transgenic for hepatitis B surface antigen (HBs-tg) received lethal irradiation and were then transplanted with C57Bl/6J male BMCs by tail vein injection. Six weeks later half the mice were treated with retrorsine, a pyrrolizidine alkaloid, to irreversibly block regeneration by endogenous hepatocytes. Mice were sacrificed at 3 and 6 months following retrorsine injections. Y chromosome containing hepatocytes were identified by in situ hybridisation (ISH), combined with phenotype markers (expression of cytokeratins 8/18, albumin, cytochrome P450, and glycogen, lack of CD45).

Results: In the control mice with chronic liver damage there was an increase in Y chromosome positive hepatocytes over time, but the proportion remained <1% of the total number of hepatocytes. However, 4.5% and 1.5% of hepatocytes had a Y chromosome in retrorsine treated mice at 3 and 6 months respectively after transplant; this compared with 0.3% in the control group. Immunohistochemistry for HBsAg combined with ISH showed 2.3% and 0.6% of hepatitis B surface antigen positive hepatocytes were Y chromosome positive at 3 months and 6 months respectively, compared with 0.5% in the control group, thus suggesting that there is some fusion occurring in this model. At 6 months but not at 3 months, we observed nodules composed of small hepatocyte like progenitor cells (SHPCs) surrounded by larger and presumably older hepatocytes. Some of these nodules expressed HBsAg while others did not. However, all of the nodules were albumin positive.

Conclusions: BMCs contribute to the regeneration of the chronically damaged liver particularly under conditions where endogenous hepatocyte replication is blocked. It appears that both transdifferentiation and fusion occur in this model. Proliferation of SHPCs appearing at 6 months may suggest that in the presence of retrorsine these cells compromise bone marrow cell engraftment in the HBs-tg mouse.

045 A PILOT SCHEME TO ASSESS THE SUITABILITY OF HAEMOCHROMATOSIS PATIENTS AS BLOOD DONORS

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Blood from patients with haemochromatosis is currently unavailable for transfusion in the UK. A potentially valuable resource is discarded because of historical concern about patient health and blood safety. The UK National Blood Service recently moved to allow asymptomatic cases

with iron overload but no liver disease to become normal blood donors. A pilot scheme was therefore set up to provide a vensection service and assess whether such a service could provide blood suitable for tranfusion to patients.

All patients with haemochromatosis undergoing regular venesection at Addenbrooke's Hospital in November 2002 and who met eligibility criteria for donation were offered to have their phlebotomy undertaken in blood transfusion. Although iron levels were monitored, anaemia (finger-prick haemoglobin) automatically safeguarded against donation. If the patient reported being unwell, phlebotomy could still be undertaken but the blood was deemed ''unsafe'' for patient use. None of the blood collected during the pilot was used for transfusion. Out of 33 patients having regular venesection at that time, 12 (36%) fulfilled criteria for blood donation. Patients who required therapeutic venesection were not referred until effective blood monitoring of iron levels was ensured for patients undergoing maintenance phlebotomy. Four subjects were subsequently withdrawn after joining and eight are still being bled. Over the one year trial period, 44 units were removed equating to 25% of overall collection for haemochromatosis patients seen in the clinic. Of this total, 40 units (91%) were potentially useable. Patients reported overall an ''excellent'' service and no problems were encountered with monitoring treatment. This pilot exercise demonstrates that it is feasible for a reasonable proportion of a haemochromatosis cohort to undergo phle botomy within the Blood Transfusion Service and contribute to the donor pool. It is hoped to extend the scheme, with national approval, to allow use of this blood when appropriate and then to other centres in the UK.

046 ROLE OF ENDOTHELIN-1 IN THE MAINTENANCE OF SYSTEMIC AND PORTAL HAEMODYNAMICS IN PATIENTS WITH CIRRHOSIS: A RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED HAEMODYNAMIC STUDY OF ENDOTHELIN-A AND ENDOTHELIN-B RECEPTOR ANTAGONISM

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Background: Endothelin (ET)-1 synthesis and receptor expression are increased in the injured liver. To date there are no studies to examine the role of ET-1 on systemic and portal haemodynamics in patients with cirrhosis.

Aims: 1) To assess the systemic and portal haemodynamic effects of selective ET-A and ET-B receptor antagonism in patients with cirrhosis; 2) to elucidate the possible therapeutic value of selective endothelin receptor antagonism in portal hypertension.

Methods: 24 studies were performed on 15 patients cirrhosis (n = 11, alcohol; n = 5, hepatitis C; mean age, 52.0 (SD 1.4) years; mean Pugh score, 6.2 (SD 0.3)). They received intravenous selective ET-A antagonist, BQ-123 (n = 8), at 1000 nmol/min and 3000 nmol/min; or selective ET-B antagonist, BQ-788 (n = 8), at 100 nmol/min and 300 nmol/min; or matched saline placebo (n = 8) in a double blind randomised manner. Haemodynamic measurements were performed through invasive pulmonary artery, hepatic venous and femoral artery catheters.

Results: BQ-123 (ET-A antagonist), compared to placebo, decreased mean arterial pressure (MAP; −15.4 (SD 10.8) mmHg, −18%, $p<0.02$), pulmonary vascular resistance index (PVRI; −122.5 (SD 85.3) dyne.sec/cm5/m2, −90%, $p<0.05$), and systemic vascular resistance index (SVRI; −1193.6 (SD 866.3) dyne.sec/cm5/m2, −17.7%, $p<0.02$), and increased heart rate (HR;+18.5 (SD 6.9) bpm,+24%, $p<0.005$). BQ-788(ET-B antagonist), compared to placebo, increased MAP (+10.5 (SD 3.33) mmHg,+12%, $p<0.03$) and SVRI (+757.4 (SD 223.6) dyne.sec/cm5/m2,+10.9%, $p<0.03$), with no effect on HR or PVRI. Both agents had no significant effects on cardiac index, hepatic venous pressure gradient, and hepatic blood flow.

Conclusions: For the first time we have shown that ET-1 contributes to the maintenance of systemic vascular tone in patients with cirrhosis. In addition, the pulmonary effects of ET-A receptor blockade suggest a possible therapeutic role in the portopulmonary hypertension.

047 A RANDOMISED CONTROLLED TRIAL OF THE USE OF ALBUMIN DIALYSIS (MARS) IN FULMINANT HEPATIC FAILURE DUE TO PARACETAMOL POISONING

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Background: Paracetamol poisoning is the commonest cause of acute liver failure in the UK with a mortality of up to 90% and, despite improvements in supportive care, the most severely affected individuals require liver transplantation in order to survive. The Molecular Adsorbent Recirculating System (MARS) is an albumin dialysis system that has been used with success in the treatment of a variety of liver diseases such as hepatorenal syndrome and acute on chronic liver failure.

Aim: To assess the value of MARS in the treatment of patients with fulminant hepatic failure (FHF). All patients had FHF due to paracetamol poisoning and all met the King's College Hospital criteria for poor prognosis, but were ineligible for liver transplant. Patients were randomised to receive either standard medical therapy (control group), or standard medical therapy + MARS treatment performed twice daily for 8–10 hours per treatment, for up to 7 days.

Results: 12 patients were randomised, control group n = 6, MARS treatment group n = 6. Survival at 7 days was significantly improved in the MARS group compared with the control group (66.6% *v* 0%, p = 0.025). The median survival in the MARS group was 8.6 days compared with 2.8 days in the control group. The requirement for inotropic support was assessed as an indicator of haemodynamic instability in these patients and there was no significant difference in the dose of noradrenaline required (90.1 mg/day MARS group *v* 97.8 mg/day control group). There was no significant difference in the number of mannitol treatments required for raised intracranial pressure between the two groups. The groups were well matched for age and sex.

Conclusions: There was a significant improvement in survival with the use of MARS in this group of patients with severe FHF. This may provide a safe and promising therapeutic intervention in patients ineligible for transplantation and in bridging those eligible for transplantation to surgery in a more stable condition.

048 ANTI-CYTOCHROME P4502E1 AUTOANTIBODY TITRE ASSOCIATES WITH IMMUNE LIVER HISTOLOGY IN ADVANCED ALCOHOLIC LIVER DISEASE

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Background: The reason why only a small proportion of heavy drinkers develop alcoholic liver disease (ALD) is still unclear. Recent work has suggested that inter individual variability in immune responses may partly explain susceptibility. As the degree of liver lymphocyte infiltration is variable in ALD, we hypothesised that patients with higher infiltration scores would have higher magnitude immune responses against antigens associated with ethanol metabolism.

Methods: Serum was collected from 51 patients with advanced ALD to determine allo-antibody titres against acetaldehyde, malondialdehyde, and hydroxyethyl radical adducts and autoantibodies against the ethanol metabolising enzyme cytochrome P4502E1. Each patient's liver biopsy was then blindly scored by two liver histopathologists for the degree of lymphocyte infiltration on a score of 1–3.

Results: 24/51 (47%) biopsies had a lymphocyte infiltration score of 1, 17/51 (33%) had a score of 2, and 10/51 (30%) had a score of 3. The means and standard deviations of antibody titres within the three groups for each of the four antigens were as follows; AcA 1, 0.25 (SD 0.17); 2, 0.32 (SD 0.20); 3, 0.35 (SD 0.24); p = 0.49, score 1 *v* 3 p = 0.27; MDA 1, 0.71m (SD 0.17); 2, 0.71 (SD 0.28); 3, 0.81 (SD 0.37); p = 0.68, score 1 *v* 3 p = 0.40; HER 1, 0.14 (SD 0.06); 2, 0.15 (SD 0.09); 3, 0.15 (SD 0.06); p = 0.90, score 1 *v* 3 p = 0.75; CYP2E1, 1, 0.66 (SD 0.28); 2, 0.68 (SD 0.40); 3, 0.94 (SD 0.42); p = 0.10, score 1 *v* 3 p = 0.03.

Conclusions: In contrast to the allo-antigens studied, significantly higher titres of autoantibodies against cytochrome P4502E1 are present in patients with a heavy lymphocyte infiltrate on biopsy than in those without. These data imply that many of the lymphocytes associating with hepatocyte injury in ALD are cytochrome P450 2E1 specific, and suggest that autoimmune responses may have a more significant role than anti-adduct responses in the pathogenesis of ALD.

049 THE GLASGOW ALCOHOLIC HEPATITIS SCORE IDENTIFIES PATIENTS LIKELY TO BENEFIT FROM CORTICOSTEROIDS

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Introduction: The use of corticosteroids in the treatment acute alcoholic hepatitis (AAH) remains controversial. Their use has been recommended

for patients with a discriminant function (DF) ⩾32. The recently described Glasgow Alcoholic Hepatitis Score (GAHS) appears to have a greater accuracy in predicting patient outcome.

Aim: The aim of this study was to asses the usefulness of the GAHS in identifying patients with AAH who might respond to corticosteroids.

Methods: Patients from two centres were studied retrospectively. All had either a clinical or histological diagnosis of AAH and DF ⩾32 on admission. The survival of patients after 28 and 84 days was assessed relative to their GAHS and whether or not they received corticosteroids.

Results: 108 patients were studied (63 Glasgow, 55 Newcastle). GAHS was ⩾9 in 60%. Corticosteroids were given to 60 patients.

Conclusions: Patients with a GAHS <9 have a good prognosis and do not appear to benefit further from corticosteroid treatment. A GAHS ⩾9 indicates a poor prognosis without corticosteroids therapy or if corticosteroids are contra-indicated.

Abstract 49 Table 1 Glasgow Alcoholic Hepatitis Score

Score value	1	2	3
Age	<50	⩾50	–
WCC (10^9/l)	<15	⩾15	–
Urea (mmol/l)	<5	⩾5	–
Bilirubin (μmol/l)	<125	125–250	>250
PT (ratio)	<1.5	1.5–2.0	>2.0

Abstract 49 Table 2 Survival

GAHS	<9	⩾9
Corticosteroid treated: day 28	86%	85%*
No corticosteroids: day 28	95%	44%*
Corticosteroid treated: day 84	71%	67%**
No corticosteroids: day 84	86%	36%**

*p<0.001; **p=0.016

050 THE INCIDENCE OF ACUTE SPORADIC HEPATITIS E IN RURAL ENGLAND

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Hepatitis E is uncommon in the developed world and largely confined to people who have travelled to endemic areas. There have been several case reports of hepatitis E in patients who have not travelled to endemic areas and some evidence to support a zoonotic source of infection in such patients.

Aim: To identify the incidence of acute sporadic icteric hepatitis E in rural England.

Methods: Retrospective analysis of case records, Hep E, IgM, IgG, and RT-PCR in patients presenting to the jaundice hotline clinic over a four year period.

Results: 572 patients with acute jaundice were seen in the study period. Of these 572, there were 42 patients with acute hepatitis where the diagnosis was unclear. All were negative for Hep A, B, C, EBV, and CMV. Of these 42, four patients were positive for Hep E IgM. Three of these patients were Hep E PCR positive. In two patients viral sequencing of a segment of the Hep E genome showed the sequence to be virtually identical with that of a UK pig strain in the genotype III group. None of these patients had travelled abroad. All patients were over the age of 50 years and non-vegetarian. Three patients made a complete recovery after 4 weeks. The fourth patient, aged 82, died at day 3 of his illness. He regularly fed his pet cat raw pigs liver: the cat died 2 months later.

Conclusions: The incidence of sporadic icteric Hep E in Cornwall, UK, is at least 0.25/100 000/year. Unlike endemic Hep E, it has a predilection for the middle aged and elderly in whom it is occasionally fatal. Viral sequencing suggests that sporadic Hep E may be a zoonosis from a pig reservoir.

051 LIVER METASTASES FROM COLORECTAL CANCER (CRC) CONSIDERED UNSUITABLE FOR RESECTION WITH CURATIVE INTENT: INTRA-OPERATIVE RADIOFREQUENCY ABLATION (RFA) IS ASSOCIATED WITH FAVOURABLE LONG TERM SURVIVAL

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Background: Complete surgical resection remains the only curative option for patients with liver metastases from CRC. Unfortunately, only 10–25% of cases are suitable for surgery with curative intent. RFA is the leading modality advocated in the management of unresectable liver metastases, in the hope of increasing resectability rates and prolonging long term survival and quality of life. The optimal route for applying RFA (that is percutaneous, laparoscopic, or open surgery) remains unclear. Such is the enthusiasm for RFA that since 2001, among 215 publications on RFA in the medical literature, only seven provide data on overall and recurrence free survival. We report here our experience of intra-operative RFA for CRC liver metastases.

Methods: Retrospective review of all patients between June 1997 and April 2001 who underwent radiofrequency ablation. All had metastases deemed unresectable for cure after discussions at our weekly multi-disciplinary GI cancer meeting.

Results: 38 patients (mean age 59.5 years; range 31–83 years) underwent intra-operative radiofrequency ablation. A total of 203 colorectal liver metastases were recorded. Of these, ablation was achieved in 168 lesions, and 35 became respectable with curative intent following RFA in 8 patients. There was no mortality. Postoperative complications occurred in five patients (13.2%). Three had undergone RFA plus resection. Ablation was considered complete in 22 patients. Median follow up was for 27.1 months (range 12–54). Among those with complete ablation, 11 patients recurred in the liver (50%), and of these one also relapsed in the pelvis, one had local recurrence, one in bone and one in lung, respectively. Overall median survival was 23 months (95% CI; 12–46). Kaplan Meier survival estimates in those with complete ablation showed 1 year, 2 year, and 3 year survival rates of 95%, 79%, and 65%, respectively.

Conclusion: This represents one of the few RFA series reporting long term outcome and complications. These results suggest that intra-operative RFA is extremely safe and effective in the treatment of patients with unresectable colorectal liver metastases. The main advantages of this technique are that it increases resectability rate, and appears to improve survival significantly.

Cell/molecular biology free papers 052–061

052 THE ROLE OF NF-κB IN BILE INDUCED CARCINOGENESIS IN BARRETT'S PATIENTS

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Barrett's oesophagus is known to be caused by chronic reflux of stomach contents. This reflux includes gastro-oesophageal reflux (GOR) and duodeno-gastro-oesophageal reflux (DGOR). DGOR exposes the lower oesophagus to bile acids, which are known to be capable of inducing DNA damage and cytotoxicity. We postulated that bile acids may promote carcinogenesis in vivo by altering the gene expression of key cancer related genes. We exposed oesophageal cells in vitro to physiological levels (100–300 μM) of the bile acid deoxycholic acid. We chose this particular bile acid as it has previously been shown by ourselves to the most reactive bile acid in terms of chromosomal damage induction. We employed cDNA membrane arrays and real time PCR to determine which genes exhibited expression abnormalities after DCA exposure. The most prominent gene expression changes induced by DCA were the switching on of the IκB and IL-8 genes. These are both transcriptional targets of the antiapoptotic factor NF-κB, suggesting activation of NF-κB by DCA. This activation of NF-κB was confirmed using a luciferase reporter system and an inhibitor of NF-κB. The involvement of NF-κB in promoting carcinogenesis in actual Barrett's patients was also assessed in biopsies taken from patients with a range

of histologies. This showed that NF-κB was indeed increasingly activated in Barrett's tissues. Interestingly, both NF-κB and IL-8 are present on chromosome 4, a chromosome shown uniquely by ourselves to be progressively amplified in Barrett's tissues during the histological progression to cancer. The activation of NF-κB by bile may provide a mechanistic basis for this chromosomal amplification, as oesophageal cells bearing extra copies of the antiapoptotic factor NF-κB are more likely to survive the cytotoxicity of bile acids in the lower oesophagus. Therefore, bile acids may well play a major role in carcinogenesis in Barrett's oesophagus and effective strategies to prevent DGOR not just GOR must be found.

053 DOWN-REGULATION OF THE HOMEOBOX GENE Cdx2 BY AN ACIDIFIED BILE PULSE IN AN IN VITRO MODEL OF BARRETT'S OESOPHAGUS

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Introduction: The homeobox gene, Cdx2, is a key regulator of development and proliferation of intestinal epithelium, directly activating intestine specific genes and exerting anti-proliferative and pro-differentiating effects in vitro (a putative tumour suppressor). We have shown that Cdx2 is neo-expressed in Barrett's metaplasia (BM) and that progression to malignancy is associated with down regulation of Cdx2.[1] We aimed to examine the effect of microenvironmental changes seen in gastro-oesophageal reflux disease upon Cdx2 expression in a columnar cell model of BM.

Methods: Cdx2 expressing LS174T cells were used as an in vitro model of metaplastic columnar cells. Subconfluent cells were exposed to a 5 min pulse of medium at pH 7 or pH 5, +/−Na Deoxycholate (0–250 μM)—to simulate a reflux event—and then grown in normal medium for 24 h. Cell viability was confirmed by trypan blue exclusion (>95% for all conditions). Cdx2 expression was monitored by immunoblotting of whole cell lysates using an anti-Cdx2 mAb. Blots were stripped and re-probed with anti-LI-Cadherin pAb (a target gene of Cdx2) and anti-gamma-tubulin Ab to confirm equal loading. Experiments were performed in triplicate. Changes in cellular localisation of Cdx2 were examined by immunofluorescence microscopy. TE7 and OE33 cells (oesophageal adenocarcinoma) were screened for Cdx2 expression.

Results: A brief pulse of acid or bile alone had little effect upon Cdx2 expression whereas a pulse of acidified bile salt significantly decreased Cdx2 abundance with a parallel decrease in LI-Cadherin. An acidified bile pulse also produced decreased nuclear immunofluorescence for Cdx2. TE7 and OE33 cells show no Cdx2 expression.

Conclusion: Acid and bile act synergistically to cause down regulation of Cdx2 in a columnar cell model of BM. In Cdx2 expressing metaplastic cells exposed to the unique environment of the distal oesophagus, down regulation of Cdx2 may act as a pro-proliferative, de-differentiating, and anti-apoptotic signal. This may be a factor favouring malignant progression.

1. **Kapoor**, *et al*. Expression of the Cdx2 homeobox protein in Barrett's Metaplasia. *Gut* 2003;**52**(S1):A42.

054 REGULATION OF PLASMINOGEN ACTIVATOR INHIBITOR 2 (PAI-2) BY *HELICOBACTER PYLORI*: ROLE IN INVASION AND IN APOPTOSIS

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Gastric adenocarcinoma is linked to infection with *H pylori*. Host, pathogen, and environmental factors probably determine whether infection progresses to cancer, but specific targets influencing the progression are unclear. Previous studies indicate that the gut hormone gastrin, which is increased in *H pylori* infection, stimulates gastric expression of plasminogen activator inhibitor (PAI)-2. The latter inhibits urokinase plasminogen activator and is increased in gastric adenocarcinoma. We have examined *H pylori* induction of PAI-2 and the effects on cell invasion and apoptosis.

Westerns blots of gastric biopsies of *H pylori* positive subjects indicated increased PAI-2 (*H pylori* negative 100 (SD 24); *H pylori* positive 199.9 (SD 22) $p<0.05$, $n=10, 12$); in *H pylori* positive subjects with plasma gastrin concentrations in the normal range, PAI-2 was still elevated. Immunohistochemistry indicated PAI-2 was localised to chief and mucus cells. In a gastric cell line (AGS cells) incubation with *H pylori* increased abundance of PAI-2 protein, and stimulated expression of 2.4 kb of the PAI-2 promoter coupled to luciferase. These effects were mediated by release of IL-8 and activation of cyclo-oxygenase (COX)-2. Video time lapse microscopy using dsRed-p65 indicated that nuclear translocation of NF-κB was associated with IL-8 and COX-2 activation, but in two different co-culture systems NF-κB was not translocated in response to paracrine stimuli. Antisense inhibition of PAI-2 expression enhanced still further *H pylori* stimulated AGS cell invasion. Moreover, in stably transfected AGS cells overexpressing PAI-2 there was inhibition of *H pylori* induced apoptosis and cell invasion, and these effects were reversed by siRNA treatment.

Conclusions: 1) *H pylori* induces PAI-2 partly via IL-8 and COX-2; 2) activation of NF-κB mediates induction of IL-8 and COX-2, but NF-κB is not a target of paracrine stimulation; 3) *H pylori* stimulation of PAI-2 inhibits apoptosis and cell invasion and is a putative host determinant of the progression to gastric adenocarcinoma.

055 EXPRESSION PATTERNS OF PROTEINS INVOLVED IN DNA DOUBLE STRAND BREAK REPAIR IN GASTRIC CANCER

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Introduction: The mammalian genome is at constant risk of mutation as a result of continually being exposed to DNA damaging agents. One particularly harmful form of DNA damage is the double strand break (DSB). DSBs repair depends on two distinct mechanisms: homologous recombination (HR) and nonhomologous end-joining (NHEJ). Inaccurate DSB repair can result in chromosomal instability and neoplastic transformation. At present, the involvement of DSB repair pathways has not been investigated in gastric cancer (GC) at all.

Methods: The expression of the key components of repair by NHEJ (Ku70, Ku80 and DNA-PKc) and of repair by HR (ATM) were investigated in 80 GC by immunohistochemistry. The percentage of positive tumour cells and the subcellular localisation of the proteins were assessed. Results were correlated with clinicopathological data.

Results: All proteins showed nuclear positivity. In all cases, more than 90% of normal gastric epithelial cells were positive for all NHEJ proteins and more than 50% were positive for ATM. In more than 85% of GC, expression of NHEJ proteins was seen in more than 70% of tumour cells. In contrast, 73% of cases showed ATM positivity in less than 25% tumour cells. Apart from a significantly higher expression of NHEJ proteins in intestinal type GC ($p=0.003$), no other correlation was found between expression of DNA DSB repair proteins and clinicopathological data.

Discussion: This is the first study investigating the expression of DNA DSB repair related proteins in GC. The most striking finding is the markedly reduced expression of ATM in the vast majority of GC. This could indicate a severely impaired capability of DNA repair by HR in GC. The higher expression of NHEJ proteins in intestinal type GC may reflect better preservation of this DNA repair pathway in this GC subtype. The regulation of DSB repair protein expression and their role in gastric carcinogenesis warrants further investigations.

056 BLOTTIN: A NOVEL TFF2 BINDING PROTEIN

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Receptors for members of the trefoil factor family (TFF) peptides remain elusive. In experiments to try and find such a molecule, we identified a novel murine TFF2-binding protein which we have named Blottin. We created a fusion protein of mouse TFF2 with secretory embryonic alkaline phosphatase (AP), expressed it in mammalian 293 cells, and probed tissue sections for binding activity using culture supernatant, visualising the AP activity directly on the sections. Substantial binding to gastric epithelium was seen, so this tissue was used in 2-D protein analytical SDS-PAGE, with PVDF western blots probed using the same ligand, and a single major protein of interest was identified by nano-LCQTOF mass spectrometry. The protein was previously unknown as a translated product, and has only mammalian homologues. The full length mRNA has been characterised by RACE in human, mouse, rat, and cow: the transcripts average 800 bp in length and show marked evolutionary conservation. The protein has a molecular weight of 21 kDa and a pI of 6.9. We prepared rabbit and mouse antibodies, and these and in situ

hybridisation for mRNA, showed high expression in surface foveolar cells of the stomach. Its intracellular location is mainly cytoplasmic, with some membrane associations. This is consistent with its N-, and particularly C-termini having hydrophobic amino acids, with the latter possessing three potential myristylation sites. No homology to known transmembrane regions exists in the molecule. SAGE analyses report that the mRNA is reduced in human gastric cancers. Functional studies are in progress to knock down Blottin expression, ascertain which signalling pathways are involved in its biology, and to elucidate the binding characteristics of the TFFs to this protein.

057 TRANSFORMING GROWTH FACTOR-BETA3 (TGF-β3) EXPRESSES ANTI-FIBROTIC PROPERTIES IN PANCREATIC STELLATE CELLS

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Introduction: Pancreatic stellate cells (PSC) play an important role in the production of extracellular matrix (ECM) in pancreatic fibrosis. In contrast to TGF-β1, TGF-β3 appears to have anti-scarring properties in cutaneous wound healing. Our study examined the role of TGF-β3 in the deposition of collagen and the balance of the metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) in PSC.

Methods: Rat PSC were used in all experiments. Collagen secretion was determined using ^{3}H-Proline incorporation collagenase assay. Procollagen type 1 and TIMP-1 mRNA levels were quantitated using real time Taqman®Quantitative PCR. MMP-9 levels were measured using gelatin zymography and MMP-2 activity was quantified with a commercial activity assay kit.

Results: Collagen secretion was significantly reduced by TGF-β3 (10, 1 ng/ml) 24 (SD 14)% and 18 (SD 14)%, respectively, compared with control. Procollagen type 1 mRNA expression was also significantly reduced with TGF-β3 compared with control. Conditioned media were examined for MMP-2 and MMP-9. There was a significant reduction in MMP-9 expression, however MMP-2 activity was increased. This phenomenon is probably explained by the reduction of TIMP-1 mRNA by TGF-β3 (10, 1 ng/ml) 34 (SD 10) % and 32 (SD 14) %, respectively, compared to control.

Conclusions: Our results suggest that TGF-β3 possesses anti-fibrotic properties in PSC 1) by reducing collagen secretion; and 2) by decreasing this potent MMP inhibitor, TIMP-1 mRNA expression. These brakes are put on the profibrotic system but from the important fibrolytic gelatinase, MMP-2 activity is increased. We believe that this is the first description of anti-fibrotic action by TGF-β3 in a non-cutaneous system.

058 NSAIDS INHIBIT OXIDATION OF GLUTAMATE IN RAT LIVER MITOCHONDRIA

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Background: Sulindac sulphide (SS), a cancer preventative metabolite of sulindac, inhibits mitochondrial oxidation of a range of metabolic substrates including fatty acids and intermediates of the tricarboxylic acid cycle. Metabolic inhibition may contribute to the anti cancer action of SS; so we have extended this work to see if other NSAIDS inhibit oxidative metabolism in liver mitochondria.

Methods: Rat liver mitochondria were prepared by differential centrifugation and ADP stimulated oxygen uptake was measured using a Clark oxygen electrode. Glutamate (10 mM) in combination with malate (2.5 mM) were used as respiratory substrates as this pair of substrates gave high oxygen consumption rates in presence of ATP (state 3) and low rates of oxygen consumption when ADP was depleted (state 4). NSAIDS including sulindac (SUL), sulindac sulphide (SS), sulindac sulphone (SF), indomethacin, (IND) (all 100 μM), salicylate (SAL), and ibuprofen (IBU) both (500 μM) were added to the electrode in state 4, then ADP was added and effects of NSAIDS on state 3 and state 4 respiratory rates was recorded. Oxygen uptake is expressed as nAtoms/min/mg protein.

Results: SS was the most effective inhibitor of respiration with indomethacin and sulindac sulphone being less effective. Salicylate, and ibuprofen had minimal effects on mitochondrial respiration even at 500 μM concentrations (see table below).

Conclusions: SS and close structural analogues (sulindac sulphone and indomethacin) were the most potent inhibitors of mitochondrial glutamate oxidation. Inhibition of mitochondrial respiration may contribute to the anti-cancer action of these compounds by causing accumulation of short chain fatty acids that promote differentiation.

Abstract 58 Effect of NSAIDS on glutamate/malate oxidation

NSAID	Con	SS	SF	SUL	IBU	IND	SAL
State 3 rate ±sem	117 ±10	36 ±4	47 ±10	76 ±7	119 ±18	74 ±4	76 ±7

(nAtoms O_2/min/mg protein Data is mean sem of 4–6 experiments).

059 *ATP8B1* VARIATIONS IN A COHORT OF WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY (ICP)

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Background: Intrahepatic cholestasis of pregnancy (ICP) is associated with prematurity, fetal distress, and intrauterine death. Homozygous mutations in the *ATP8B1* gene cause cholestasis with a normal serum gamma-glutamyl transpeptidase, and have been reported in two forms of cholestasis; progressive familial intrahepatic cholestasis type 1 and benign recurrent intrahepatic cholestasis. The role of *ATP8B1* in the aetiology of ICP is not known. We aimed to establish whether mutations in *ATP8B1* are associated with ICP.

Methods: The coding exons of *ATP8B1* were sequenced in 11 cases of ICP with normal serum gamma-glutamyl transpeptidase. The frequency of the sequence variants that were identified was studied in a total of 180 ICP cases and 120 controls. In vivo hepatic 31P magnetic resonance spectroscopy (MRS) was also used to establish whether one *ATP8B1* mutation was associated with metabolite abnormalities in the liver.

Results: Sequence analysis identified two heterozygous *ATP8B1* transitions (208G>A and 2599C>T) that resulted in amino acid substitutions in four ICP cases. 208G>A, was present in three unrelated cases. MRS was performed in two of these cases and demonstrated a marked increase in the phosphodiester signal and a reduction in the NTP (nucleotide triphosphate) signal in both patients.

Interpretation: This is the first demonstration of *ATP8B1* mutations in ICP, and the variants reported cause a new phenotype for mutations in this gene. The MRS studies in women with the D70N mutation suggest that this variant is associated with a relative rise in biliary phospholipid and reduced hepatic NTP levels. These data also suggest that MRS can be used for non-invasive assessment of the liver and biliary constituents in cholestasis.

060 TRANSCRIPTOME ANALYSIS OF THE HUMAN COLON CANCER CELL LINE CaCo2 FOLLOWING EXPOSURE TO SULFORAPHANE REVEALS P21 AND KLF4 MEDIATE CELL CYCLE ARREST AND DIFFERENTIATION

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Sulforaphane (4-methylsulfinylbutyl isothiocyanate), obtained from the consumption of broccoli, has been implicated as a potentially important dietary anticarcinogen. It has been reported to be a potent inducer of phase II detoxification enzymes, and to induce expression of genes associated with cell cycle arrest and apoptosis in both cell cultures and animal models. To further investigate the bioactivity of sulforaphane, particularly with regard to cell cycle regulation, we quantified gene expression in CaCo-2 cells following exposure to a range of physiologically appropriate concentrations of sulforaphane (1–50 μM) via affymetrix oligonucleotide arrays and real time PCR. Cell cycle progression and apoptosis was quantified via flow cytometry and annexinV/propidium iodide staining. Following treatment with 50 μM sulforaphane, 125 genes were upregulated and 81 downregulated ($p<0.001$), the majority in a dose dependent manner. As expected, these genes could be assigned to a variety of functional clusters, including xenobiotic metabolism, apoptosis, and cell cycle regulation. Within this latter class, upregulation of p21 (CDKN1A), GADD45β and down regulation of MCM4 and MCM7 were consistent with cell cycle suppression. We also observed induction of Krüppel-like factor 4 (KLF4), a transcription factor implicated in suppressing cell cycle and anti-proliferation activity, partially via p21 induction, and in differentiation

of intestinal cells, particularly terminal differentiation of goblet cells. We found no evidence of KLF4 induction being itself mediated by CDX-2, which was not induced, in contrast to other reports. Epidemiological evidence suggests that consumption of fruits and vegetables reduces the risk of cancers of the gastrointestinal tract. We envisage a fine balance within intestinal crypts of cell proliferation, apoptosis and differentiation, which is partially modulated by dietary factors, including human metabolites of phytochemicals from fruit and vegetables. Many of these have been shown to induce apoptosis. In contrast, our data suggest that sulforaphane may be important in reducing proliferation and promoting differentiation. Further studies on KLF4 induction by sulforaphane and its implications for cellular differentiation are in progress.

061 THE SOURCE OF *WNT* EXPRESSION IN THE COLON; SUBEPITHELIAL MYOFIBROBLASTS AND THE MAINTENANCE OF THE STEM CELL NICHE

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Background: *Wnt* signalling is known to play an important role in the various stages of embryogenesis and carcinogenesis; recent reports have implicated that *Wnt* proteins could act as growth factors, maintaining the stem cell phenotype and even controlling the symmetry of stem cell divisions (Yamashita. *Science* 2003;**301**:1547–50). The *Wnt* family consists of 19 different genotypes in humans and the mouse. It is now known that nuclear expression of β-catenin/TCF, which is up-regulated by *Wnt* protein, is confined to the bottom of normal colonic crypts (van de Wetering. *Cell* 2002;**111**:241–50). However, the source of the *Wnt* signalling and its regulation is obscure. Colonic sub-epithelial myofibroblasts (SEMFs) are present immediately beneath the basement membrane, just under the epithelial cells and speculation is rife that these maintain the stem cell niche (Brittan. *Gut* 2002;**50**:752–7). In this study we show that contribution of SEMFs are the source *Wnt* signalling in the colon.

Method: Colonic SEMFs and colonic epithelial cells were isolated from wild type C57 mice and from IL-$10^{-/-}$ mice (which show active colitis) using previously reported methods, and the expression of *Wnt* mRNA was studied using RT-PCR and *in situ* hybridisation.

Results: RT-PCR studies revealed 1) *Wnt*3a mRNA is strongly expressed in colonic SEMFs, but not in epithelial cells; 2) *Wnt5*a mRNA expression is observed both in colonic SEMFs *and* epithelial cells; and 3) the expression of *Wnt5*a is attenuated in epithelial cells from the IL-$10^{-/-}$ mouse.

Conclusion: 1) *Wnt*3a derived from SEMFs regulates the expression of β-catenin/TCF in crypt epithelial cells and may maintain stem cell phenotype; 2) the attenuated *Wnt5*a expression in IL-$10^{-/-}$ epithelial cells could be a consequence of inflammation, suggesting that cytokines might also modulate stem cell behaviour. The source of *Wnt* signalling in the colon is predominantly from the SEMFs, confirming a role for these cells in the maintenance of the stem cell niche.

Colorectal free papers 062–071

062 ROLE OF CYTOKINE GENE POLYMORPHISMS IN COLORECTAL CANCER AND THEIR INTERACTION WITH ASPIRIN USE IN THE NORTH EAST OF SCOTLAND

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Background and Aims: Chronic inflammation increases the risk of many malignancies including colorectal cancer (CRC). This risk is reduced significantly by regular use of COX inhibitors such as aspirin and NSAIDs, suggesting that inflammation plays a key role in the pathogenesis of CRC. There is strong evidence that pro-inflammatory cytokine gene polymorphisms increase the risk of several cancers including gastric adenocarcinoma. The aim of this study was to evaluate the role of pro- and anti-inflammatory cytokine gene polymorphisms in CRC in the north east of Scotland, and to study their interaction with regular aspirin use.

Methods: We assessed polymorphisms in the *IL-1, IL-10, TNF-A*, and *TGF-B* genes in a population based case control study of CRC cases (n = 263) and frequency matched controls (n = 408). Odds ratios (ORs), adjusted for age and sex, were calculated for each polymorphism and combinations of polymorphisms. In addition joint effects of genotype and regular use of aspirin were analysed.

Results: There was no significant association between any of the cytokine polymorphisms and CRC risk, either alone or in combination. There was a statistically significant (p = 0.032) interaction between the pro-inflammatory *IL-10-592* A allele and aspirin use, with a 50% reduction in CRC risk in carriers of this allele who were on regular aspirin. For the other polymorphisms, regular use of aspirin was associated with a lower risk of disease, irrespective of genotype.

Conclusions: The studied polymorphisms had no effect on risk of CRC in this population. However, the chemoprotective effects of aspirin appear maximal in those who have a pro-inflammatory IL-10 genotype. This finding calls for further assessment of the role of host genetic factors in CRC and their interaction with chemopreventive agents.

063 EX VIVO SENTINEL LYMPH NODE MAPPING IN COLORECTAL CARCINOMA. A NOVEL APPROACH THAT IDENTIFIES OCCULT TUMOUR SPREAD

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Background: The development of systemic disease after curative surgery for colorectal cancer approaches 30%. This may represent understaging. Sentinel lymph node mapping (SLNM) identifies lymph nodes at high risk of harbouring metastatic disease. We established a novel *ex vivo* mapping technique that is easily applicable both in theatre and also during histological processing.

Methods: With full ethical approval and informed consent, 27 patients with primary colorectal cancer and 3 patients with severely dysplastic tubulovillous adenomas prospectively underwent *ex vivo* SLNM. 1–2 ml of isosulphan blue dye was injected around and into tumours within 5–10 minutes of resection. Specimens were then placed in formalin. While specimens were processed routinely, blue stained nodes were noted and subsequently underwent step sectioning. H+E and cytokeratin staining was then performed.

Results: An average of 15 lymph nodes (range 2–37) were identified in each specimen. Sentinel nodes were found in all 30 patients (100%) with an average of 4 sentinel nodes per patient (range 1–7). In 9 of 15 (60%) Dukes C patients, at least one sentinel node was found to contain metastatic tumour on routine reporting. This was adjusted to 11 of 15 after step sectioning (73%). Three of the 4 Dukes C patients in which sentinel nodes were falsely positive had undergone neoadjuvant radiochemotherapy for locally advanced rectal cancer. Focused examination identified occult micrometastases in the sentinel nodes of two Dukes A patients (n = 4) and in three Dukes B patients (n = 8).

Conclusion: *Ex vivo* SLNM is a complication free technique that is poorly described in the literature. Our findings confirm that *ex vivo* SLNM is feasible in all types of colorectal cancer, except in patients treated with neoadjuvant radiochemotherapy. Moreover, the technique is readily introduced into hospital practice and identifies occult tumour spread.

064 ACCURACY OF HISTOPATHOLOGY REPORTING IN COLORECTAL CANCER (CRC): WE NEED A PROFORMA

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Introduction: The quality of a histopathology report in CRC will determine prognosis and the need for adjuvant therapy. This study evaluated the completeness of pathology reports in 82 consecutive patients (rectal cancer 47; colon cancer 35) based on the Minimum Data Set by the Royal College of Pathologists, UK.

Methods: The pathology reports were reviewed by a single person who looked for 17 pathology data sets for colon cancer and 15 for rectal cancer. Completeness of reporting (%) was classified as 40–50%, 60–70% or 80–100%.

Results: See table. Tumour involvement at resection margin was reported in 91.5%. Information on distance from tumour to distal resection margin was present in 68% of reports. However, involvement of the apical node was commented only in 33% of reports.

Conclusion: There is wide variation in the quality of pathology reporting in colorectal cancer. We have found a lack of vital data in up to two third of reports. We believe a standerdised report format will ensure complete pathology reporting in CRC.

Abstract 64

Complete report % (Royal College of Pathology standard)	Rectal cancer n=47	Colon cancer n=35	Total
40–59%	05 (11%)	04 (11.5%)	09
60–79%	23 (49%)	13 (37%)	36
80–100%	19 (40%)	18 (51.5%)	37
Total	47	35	82

065 THE EFFECT OF METHOXAMINE ON ANAL SPHINCTER TONE IN VITRO: A POTENTIAL TREATMENT FOR INCONTINENCE

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Introduction: Pharmacological manipulation of the anal sphincter with α_1-adrenoceptor agonists may improve function in patients with passive faecal incontinence. Topical phenylephrine causes a significant rise in resting anal pressure in incontinent subjects, but at high concentrations can cause side effects. This study examines the effects of racemic methoxamine, L-*erythro* methoxamine (its synthetic stereoisomer), and phenylephrine on sheep internal anal sphincter (IAS) tone *in vitro*.

Methods: Using a validated model, strips of sheep IAS were suspended in isolated organ baths. Paired segments were exposed to increasing concentrations of racemic methoxamine, L-*erythro* methoxamine, and phenylephrine to construct dose response curves. Prazosin (an α_1-adrenoceptor antagonist) was added at the end of each experiment. Results are expressed as mean (s.e.m).

Results: Phenylephrine and racemic methoxamine caused an increase of 113 (12) *v* 159 (27) % in baseline tone at 30 μM concentration ($n=14$), with little effect seen at 0.1–1 μM. The negative logarithms of the concentration required for a 50% increase in baseline tone for phenylephrine 5.31 (0.13) M and racemic methoxamine 5.42 (0.17) M were comparable. L-*erythro* methoxamine caused an increase of 197 (18) % in baseline tone at 30 μM ($n=18$). The negative logarithm of the concentration required for a 50% increase in baseline tone for the stereoisomer was significantly lower than for phenylephrine or the racemate 6.52 (0.13) M ($p<0.05$). The addition of 0.3 μM prazosin reduced baseline tone to under 20% of that induced by all agonists.

Conclusions: L-*erythro* methoxamine has a contractile effect on IAS, mediated via α_1-adrenoceptors, which is 10-fold more potent than racemic methoxamine and phenylephrine in vitro. L-*erythro* methoxamine is likely to be more effective than phenylephrine at increasing anal tone in vivo, at lower concentrations which would minimise side effects. Clinical trials are now underway in this regard.

066 POLYMORPHISM OF THE MTHFR GENE IS ASSOCIATED WITH ALTERED GENE EXPRESSION IN COLORECTAL CANCER

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Aims: Folate supplementation appears to reduce colorectal cancer (CRC) risk. CRC risk is also modulated by the C to T polymorphism at position 677 of the methylenetetrahydrofolate reductase (MTHFR) gene, which results in a thermolabile variant of MTHFR and is associated with reduced cellular folate levels. The aim of this study was to evaluate the relationship between MTHFR expression in colorectal tumour tissue and the C677T polymorphism.

Methods: 39 patients with colorectal cancer were studied. DNA was extracted from citrated blood and tumour tissue and genotyped for the MTHFR C677T polymorphism. Expression of MTHFR in colorectal tumour tissue and normal colonic mucosa from the same patient was quantified by real time PCR. Hypothesis testing was performed on ranks of the ratio of MTHFR expression to 18S. The analysis of variance model was used to test whether interactions with genotype were significant.

Results: Overall expression of MTHFR was not significantly different in tumour tissue compared to normal colonic mucosa ($p=0.24$). However, when genotype was taken into account, a statistically significant reduction in MTHFR expression was observed in tumour *v* normal tissue from T carriers ($p=0.04$) but no difference was observed in CC homozygotes. 73% of the eighteen T carriers showed reduced expression of MTHFR in tumour tissue compared to 33% of the 21 CC homozygotes.

Conclusions: Lowered MTHFR expression may contribute to colorectal tumorigenesis among carriers of the T allele at position 677 of MTHFR. This finding suggests that the T carrier subpopulation may benefit more from folate supplementation. The study also illustrates the importance of considering genotypic covariates in the analysis of changes in gene expression involved in carcinogenesis.

067 DIFFERENTIAL EXPRESSION OF GAMMA-CATENIN (PLAKOGLOBIN) IN COLORECTAL CANCER FOLLOWING COX-2 INHIBITION

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Aims: γ-Catenin (Plakoglobin) is a member of the catenin family. It functions in cell adhesion and the WNT signalling pathway. Defects in both WNT signalling and COX-2 expression play important roles in colorectal cancer. The aim of this study was to characterise γ-catenin expression in colon cancer, and to examine the effects of COX-2 inhibition on γ-catenin expression.

Methods: Gene expression studies were carried out by quantitative (real time) RT-PCR. Western blots were performed using a monoclonal antibody to γ-catenin (Becton Dickenson) and immunohistochemistical staining was performed using a polyclonal antibody to γ-catenin (SantaCruz).

Results: γ-Catenin is highly expressed in the HCA-7 cell line, which is characterised by constitutive COX-2 expression. Treatment of this cell line with SC 236 (selective COX-2 inhibitor), caused a reduction in γ-catenin transcription which was maximal at 8 hours (mean reduction 1.85 fold, SEM +/− 0.23) and was rescued by co-treatment with a PGE2 analogue. This was accompanied by a similar reduction in protein expression by western blot analysis ($n=3$). γ-Catenin expression was up regulated in 50% of human colorectal tumours examined ($n=18$), compared with adjacent normal mucosa (mean fold difference for tumours showing an increase 2.9 fold, SEM+/−0.4). This trend was confirmed by immunohistochemistry ($n=9$). Epithelial staining for γ-catenin and COX-2 correlates in tumour tissue.

Conclusions: γ-Catenin expression is upregulated in colorectal cancer. This may represent a downstream effect of COX-2 over expression. Further evaluation of this pathway may facilitate better understanding of the disease and development of anti-cancer therapies.

068 HIGH DENSITY OLIGONUCLEOTIDE ARRAYS DEMONSTRATE DIFFERENTIAL GENE EXPRESSION IN COLON CANCER CELLS FOLLOWING COX-2 INHIBITION

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Aims: COX-2 plays a crucial role in colorectal carcinogenesis and selective COX-2 inhibitors have been shown to have antineoplastic effects in vitro and in vivo. The precise mechanisms underlying these effects has yet to be established. The aim of this study was to elucidate some of the downstream effectors of COX-2 in colon cancer using high density oligonucleotide arrays to evaluate differential gene expression in a colon cancer cell line following treatment with a COX-2 inhibitor.

Methods: Pooled RNA was extracted from HCA-7 controls or cells treated for up to 8 hours with SC-236 (5 mol). Samples were hybridised to the Affymetrix U95 Gene Chip, a high density oligonucleotide array with over 12 000 probe sets. Hybridisations were preformed in triplicate. Vectors for the change in expression of each gene were calculated; these were used to select consistently differentially expressed genes. Validation of differential gene expression was by quantitative RT-PCR.

Results: 110 genes were identified as being consistently differentially expressed in response to COX-2 inhibition. Ontology analysis revealed that many of these genes are involved in regulation of cell proliferation, signal transduction, and apoptosis. Differential expression of several genes has been validated by quantitative RT-PCR. Upregulation of several transcription factors, including COPEB, suggests alterations in TGF signalling in response to COX-2 inhibition.

Conclusions: Analysis of differential gene expression by high density oligonucleotide arrays highlights possible downstream effectors of

COX-2 in colorectal cancer, including differential expression of genes that are important in TGF signalling pathways.

069 COLORECTAL SYMPTOMS IN THE COMMUNITY—A TICKING TIME BOMB?

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Introduction: Current guidelines dictate that patients with high risk colorectal symptoms should be referred and seen in secondary care within 2 weeks. Screening is to be implemented, and with increasing awareness there may be an added workload. We have assessed the prevalence of significant symptomatology in the general population and the relationship of these symptoms to the NHS guidelines for urgent referral.

Methods: A randomly selected cross section of 487 people, between the ages of 50 and 80, from one general practice were included in this study. They were each sent and asked to return a patient consultation questionnaire (PCQ), a comprehensive 4 page document with detailed questions regarding the presence of specific colorectal symptoms. Non-responders were followed up with a reminder and second PCQ. Symptoms data were analysed and the NHS guidelines for urgent referral applied.

Results: The total response was 411 (84.4%) returned PCQs. The overall prevalence of symptoms was 43.9%. PR bleeding, change in bowel habit, abdominal pain, and peri-anal symptoms individually had a prevalence of 15.6%, 19.9%, 20.5%, and 22.4%, respectively. There were significantly higher levels of symptoms in the 279 (57.3%) who returned the first PCQ, indicating increased initial compliance in symptomatic members of the population. Applying the NHS guidelines for urgent referral from primary to secondary care to the respondents classified 12% of the population as fulfilling the criteria.

Conclusion: There is a high prevalence of symptoms in the general public. There is a need to improve on the specificity of the priority assessment tool if we are to avoid overwhelming available resources.

070 FOUR YEARS EXPERIENCE OF AN ALGORITHM FOR COLORECTAL REFERRALS

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Introduction: Demand beyond capacity and introduction of the 2 week rule have stimulated original ways of prioritising colorectal referrals.

Methods: A patient consultation questionnaire (PCQ), completed by the patients themselves, was devised in 1998. An algorithm based on 17 factors in the PCQ produced a weighted numerical score (WNS) prior to starting the study. From Oct 1999 all patients referred to a surgical colorectal unit with primary colorectal symptoms had a WNS generated by the above algorithm from the PCQ. The minimum investigation was a flexible sigmoidoscopy. The relationships between the score and the outcome diagnosis have been assessed for this 4 year period. Statistical significance was assessed by the *t* test and χ^2 square test. Discriminatory Power was assessed using Area Under the Receiver Operator Characteristics (ROC) (AUC).

Results: Of the 5099 patients, 210 (4.1%) had colorectal cancer (CRC). The WNS was effective in detecting cancer. The average score of cancer patients (72, 95% CI (69 to 75)) was significantly higher than non-cancer patients (45, 95% CI (44 to 45)), $p<0.001$. The WNS had a very powerful discriminatory power as demonstrated by the high AUC of the ROC curve (0.80). At a similar cancer detection rate the WNS required lower numbers of referrals to be graded as urgent (40%) in comparison to the current NHS guidelines if implemented to perfection (49%) ($p<0.0001$). The WNS not only separated out the cancer from the benign patients, but also accurately categorised the disease profiles within the benign diagnostic groups.

Conclusions: The PCQ is dependent on history alone and is easily reproducible. In conjunction with the WNS, which removes operator bias, it is as an accurate system for the prediction of patients with symptomatic colorectal cancer and provides a tool for demand management and referral protocols.

071 PERCUTANEOUS ENDOSCOPIC COLOSTOMY (PEC)—ROLE IN RECURRENT SIGMOID VOLVULUS AND CHRONIC CONSTIPATION

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Introduction: Percutaneous endoscopy colostomy (PEC) is a relatively new technique with several indications. We have employed the technique to treat patients with recurrent sigmoid volvulus (RSV) and chronic constipation (CC).

Methods: Patients having failed standard methods of conservative treatment for recurrent sigmoid volvulus and chronic constipation were considered for PEC. The technique used is very similar to the ''pull method'' of PEG insertion. A site in the abdomen is identified by transillumination via flexible sigmoidoscopy. The PEC is then used to flush the colon in CC, and in RSV fixes the colon to prevent recurrence. In the constipation patients, symptom and Quality of Life (QoL) scores were assessed pre and post PEC using symptom scores and SF-36 and GIQLI systems.

Results: To date we have performed 22 PECs on 19 patients (13 for CC (12 left colon, 2 right colon) and 8 for RSV). There were no immediate significant complications. Median follow up is 8 months (range 1–26). In the RSV group 1 PEC was removed for site infection and the volvulus recurred 48 hours later. There has been no other recurrent volvulus. There were functional improvements in symptoms, transit study results and QoL scores in the CC group. However, site infection has been a significant problem in CC requiring removal of 7 PECs.

Conclusions: Our experience suggests that PEC is an effective treatment option for RSV, especially in the frail patient who presents a significant operative risk. However, despite functional improvement in CC patients, we have encountered significant problems with infections of the PEC site in this group resulting in removal of the tubes.

Neoplasia free papers 072–081

072 BONE MARROW CONTRIBUTES TO TUMOUR STROMA

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Background: There has recently been much excitement in the field of stem cell biology as adult bone marrow derived cells have been shown to have a greater degree of plasticity than previously thought. We have previously shown that bone marrow can contribute to myofibroblast populations in the mouse and human gut, and very recently that the bone marrow contribution to myofibroblast and fibroblast populations is a more generalised phenomenon, which is exacerbated by injury. We now report that the bone marrow also contributes to tumour stroma.

Method: RIPTag (rat insulin promoter large T antigen) mice develop β cell tumours of the pancreas after approximately 9 weeks of age. Female RIPTag mice were transplanted with male wild type littermate bone marrow. Mice were killed on the development of signs of distress—indicating the development of symptomatic tumours. The fate of the bone marrow derived cells was followed by detection of the Y chromosome by in situ hybridisation, combined with immunohistochemistry for myofibroblast markers such as smooth muscle actin (αSMA). We also had samples from patients who developed tumours after sex mismatched bone marrow transplant, which were analysed in the same way.

Results: Approximately 25% of myofibroblasts were found to be bone marrow derived in pancreatic tumours post sex mismatched bone marrow transplant. These tended to be concentrated within 1 high power field of the tumour edge ($p<0.05$). We have also found evidence of donor cells in human tumours post sex mismatched bone marrow transplant. These cells await full characterisation.

Conclusion: The bone marrow appears to have a far more dynamic role in the response to injury than previously suspected. The contribution of the bone marrow is a further illustration of the interaction of the bone marrow cells with other tissues, including tumours. This may lead to the development of new avenues for therapy.

073 HGF/MET INCREASES THE ANCHORAGE INDEPENDENT GROWTH OF OESOPHAGEAL ADENOCARCINOMA CELLS

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Background: Oesophageal adenocarcinoma develops along the Barrett's metaplasia–dysplasia–adenocarcinoma sequence. The hepatocyte growth factor (HGF) receptor MET, shows increased expression along this sequence and patients with cancers that overexpress MET exhibit poorer short term survival. We have shown previously that MET

activation downregulates the cell adhesion molecule, E-Cadherin. We sought to investigate a link between MET activation and cell survival and growth.

Aims: To investigate the effect of MET activation on cell cycling and the ability of oesophageal cell lines to form colonies in agar gel.

Methods: Two cell lines that express MET (OE33, SEG1) and a cell line that does not (TE7) were used. Cells were grown in flasks to 50% confluence then incubated with HGF at 100 ng/ml at time points 2 hrs and 24 hrs. Nuclei were stained with propidium iodide and flow cytometric analysis was then used to quantify the effects of HGF on cell cycling. Trypsinised cells were seeded at 5×10^3/ml into agar containing fetal calf serum and HGF at 100 ng/ml. The number of colonies (>50 cells) per well were counted at day 10. Unstimulated cells were used as control groups.

Results: None of the cell lines showed a significant change in the number of cells in S phase in response to HGF. OE33 and SEG1 showed 37% and 20% increases respectively in agar colony formation when grown with HGF ($p<0.01$). TE7 (which lacks the MET receptor) were unable to form colonies in agar.

Conclusions: MET activation increases the ability of cells to survive in an adhesion independent environment. This may be important in the process of lymphatic spread and metastasis formation and MET may be a prognostic marker in this regard. An inhibitor of MET may be effective in the treatment of oesophageal adenocarcinoma.

074 THE PRESENCE OF FAT COUNTERACTS THE ABILITY OF VITAMIN C TO PREVENT ACID *N*-NITROSATION

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Introduction: Nitrite is a pre-carcinogen as it can be converted to nitrosative species and *N*-nitroso compounds by acidification in the presence of thiocyanate. The optimum site of acid nitrosation is the gastro-oesophageal (GO) junction where nitrite and thiocyanate secreted in saliva first encounter acidic gastric pH. The most important factor preventing this nitrosative chemistry is vitamin C, which converts the nitrosating species to nitric oxide. However, in the presence of fat, nitric oxide reacts with oxygen to reform nitrosative species.

Aim: To assess the effect of the presence of fat on nitrosative chemistry under conditions simulating the GO junction.

Methods: Nitrite (100 μM) and thiocyanate (1 mM) were added to 50 ml 0.1 M HCl pH 1.5 in the presence and absence of vitamin C (1 mM) and presence and absence of 5 ml of the lipid tributyrin. The nitrosatable secondary amine morpholine was added to the aqueous and lipid phases at a concentration of 5 mM. The concentration of *N*-nitrosomorpholine present in the aqueous phase at 15 min was analysed by GCMSMS. Each experiment was conducted on six occasions.

Results: In the absence of the lipid, 6.3 (SD 0.8) μM *N*-nitrosomorpholine was generated in the aqueous solution when no vitamin C was present but no *N*-nitrosomorpholine formed in the presence of vitamin C. With the globule of lipid present, 4.8 (SD0.7) μM *N*-nitrosomorpholine was detected in the absence of vitamin C. However, when lipid was present the addition of vitamin C did not prevent *N*-nitrosomorpholine formation with 4.3 (SD 0.4) μM being detected in the aqueous phase at 15 min.

Conclusion: Lipid counteracts the ability of vitamin C to prevent acid nitrosation. This can be explained by the vitamin C converting nitrite to nitric oxide and the latter generating *N*-nitrosomorpholine within the lipid, which can diffuse back out into the aqueous phase. The lumen of the cardia of the stomach has the highest lipid content due to the fact that most lipids float and this may be a factor in the nitrosative chemistry occurring at this particular anatomical site.

075 FLAT ADENOMAS IN THE COLON ORIGINATE IN MONOCRYPTAL ADENOMAS AND CLONALLY EXPAND BY SUPERFICIAL BUDDING WITHOUT SIGNIFICANT ''TOP DOWN'' SPREAD

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Introduction: Controversy exists concerning the mode of expansion of colorectal adenomas. The Vogelstein group champion the ''top down'' theory—lesions arise and grow across the mucosal surface and down into the crypts, whereas our group propose bottom up spread. Top down spread is said to be the mode of expansion of flat adenomas.

Methods: 55 flat adenomas from 10 patients were stained with H&E, and by immunohistochemistry for Ki-67 and MCM2, for β-catenin, CD44, and carbonic anhydrase II to detect both β-catenin/Tcf/Lef-dependent and independent transcription targets.

Results: We found that: 1) flat adenomas of all sizes, while spreading predominantly in the superficial part of the mucosa, all contain dysplastic crypts which reach the muscularis mucosa; 2) laterally, there are superficially placed crypts which grow down between existing normal crypts, which show extensive budding and fission events; 3) in these crypts, most proliferative cells are found towards the top, reversing the usual distribution of normal crypts; 4) cells with nuclear β-catenin which are MIB-1 and MCM2 positive seem to grow over the surface of the mucosa; but 5) top down spread occurred rarely.

Conclusions: These findings suggest that: 1) flat adenomas originate in monocryptal adenomas; 2) adenomatous cells migrate across the surface giving rise to new adenomatous crypts which grow downwards, dissecting and isolating adjacent normal crypts; 3) these new crypts then expand by crypt fission and branching; 4) unlike early tubular adenomas, most proliferative cells are found in the superficial portion of these new crypts; and 5) top down spread is rare. Flat adenomas thus show a mode of clonal expansion, which differs diametrically from tubular adenomas, which probably reflects a much different molecular pathology.

076 EFFECTS OF DIETARY FIBRE ON POLYP FORMATION, CELL PROLIFERATION AND CRYPT FISSION IN THE *MIN* MOUSE

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Introduction: 90% of all colon cancer is environmental, mostly due to diet and lifestyle. It has long been believed that high fibre diets are a ''good thing'' and are protective against colorectal cancer. This has induced food industries to promote synthetic fibres to be added to food, termed as ''functional foods'', aimed to be beneficial to health. However, some animal studies and human epidemiological studies have indicated the converse. The role of fibre in cancer is complex and literature has shown that these effects maybe attributed to use of different types of fibre and other fermentable substrates. Fermentation products stimulate cell proliferation and can be a cancer risk.

Aim: to investigate the actions of specific fermentable fibre substrates on polyp development in the *Min* mouse.

Method: *Min* mice model (C57BK/6J-ApcMin) was used as this has a loss of APC gene function resulting in multiple intestinal polyps, making it an ideal model for testing dietary factors and their effects on tumour progression. 10 four week female *Min* mice were used for each group and fed a chow diet, semi synthetic diet, or semi synthetic supplemented diets with cellulose, wheat bran, or apple fibre for 8 weeks. Carnoy's fixed tissue was viewed under the microscope and scored for polyp number and tumour burden. Stained tissue was microdissected to score for cell proliferation and crypt fission.

Results: there were significant increases in polyp number in the proximal third of the small intestine with bran or apple fibre. The action of apple fibre was seen throughout the small bowel and the mean number of polyps in the small intestine of the apple group was 99.2 (SD11.1) *v* 40.0 (SD 8.2) for the control semi synthetic diet group ($p<0.004$). Significant increases in tumour burden were seen with apple fibre in the small intestine and with bran in the colon where tumour burden increased from 8.1 (SD 3.1) to 33.6 (SD 6.7) mm^3 ($p<0.01$).

Conclusion: The most fermentable fibre was apple, which more than doubled polyp number, tumour burden, and altered crypt fission. Wheat bran markedly increased the size and volume of the polyps in the colon. Different fibres have different fermentation rates and the products of fibre fermentation can stimulate cell proliferation in vivo and may be, therefore, a risk factor for tumour formation.

077 CHROMOSOMAL CHANGES IN COLORECTAL ADENOMAS: RELATION TO GENE MUTATION AND CLINICAL UTILITY AS A MARKER OF SYNCHRONOUS NEOPLASIA

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We have previously shown that the conventional model of colorectal carcinogenesis (Vogelstein) involving sequential changes in the APC,

K-ras and p53 genes is not supported by the mutational profile of cancers (*PNAS* 2002;**99**:9433). We have also demonstrated specific associations between gene mutations and chromosomal abnormalities (for example, p53 with 20q+, 18q−, 13q+, K-ras with 12p+. *Cancer Res* 2003;**63**:4656).

We have now analysed APC, K-ras and p53 mutations and chromosomal change by comparative genomic hybridisation (CGH) in 79 colorectal adenomas. APC (52%) and K-ras (27%) mutations were seen at a similar frequency to that observed in cancer. p53 mutation (3 cases, 4%) was rare. As in cancers, we did not see any cases with both K-ras and p53 mutation supporting our previous contention that these mutations may define separate pathways to colorectal carcinoma. Many of the important CGH changes seen in cancer were also present in adenomas. Some (for example, 12p+) were seen at similar frequency in cancers and adenomas. The two most frequent cancer changes, 20q+ (80%) and 18q- (76%), were much less common in adenomas (11% and 10%, respectively). However, both abnormalities were significantly associated with histological severe dysplasia ($p<0.01$) and with p53 mutation ($p=0.03$). Other clinically relevant associations include 12p+, which was more common in rectal (as opposed to colonic) lesions ($p<0.05$). 12p+ was also linked to K-ras mutation ($p<0.01$) and large size of adenoma ($p<0.01$). 13q+ was seen significantly more commonly in patients with synchronous neoplasms (more than one adenoma or adenoma plus carcinoma, $p<0.05$). This finding may have particular implications in follow up of adenoma patients and in cancer screening programmes.

This study shows that specific chromosomal amplification and deletion (not currently included as part of the prevailing models of tumourigenesis) interact in complex ways in colorectal adenomas and carcinomas. Some of the changes show great promise of clinical utility. Follow up studies are underway.

078 COLONIC CRYPT STEM CELL MUTATION INDICES (CCSCMI) IN A PREDICTIVE RISK ASSESSMENT MODEL FOR DIET RELATED CHEMICALS

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Background: Humans are exposed to mixtures of harmful chemicals from diet and lifestyle but cancer risk assessment is hampered by the lack of a mechanistically based predictive model. We test the hypothesis that crypt stem cell mutation indices (CCSCMI) may provide the scientific basis for a risk assessment model that is predictive of colonic tumour formation.

Methods: N-methyl-N-nitrosourea [MNU] and undegraded lambda carrageenan (λCgN) were tested as model diet related chemicals alone or within a mixture, upon CCSCMI in 90 female Balb/c mice. The predictive power of CCSCMI induced by chemical treatment was tested against later colonic tumour formation represented by aberrant crypt foci (ACF), at 20 weeks after treatment.

Results: Combined λCgN/MNU treatment regimens were associated with greater total crypt stem cell mutation load ($p<0.01$), greater mutant patch formation ($p<0.05$), greater numbers of large mutant patches ($p=0.002$), greater number ($p<0.001$) and size ($p<0.01$) of ACF, than MNU alone. Linear correlations were observed between total crypt stem cell mutation load and number ($r=0.732$; $p<0.01$) and size ($r=0.84$; $p<0.01$) of ACF.

Conclusions: CCSCMI induced by diet related chemicals are predictive of later colonic tumour formation and may provide the scientific basis for a risk assessment model. The model may improve understanding of interactive mechanisms of dietary chemicals, within mixtures. Information gleaned may aid cancer prevention.

079 THE PROGNOSTIC SIGNIFICANCE OF K-RAS, P53, AND APC IN COLORECTAL ADENOCARCINOMA

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It has been proposed that accumulation of mutations in several genes contributes to colorectal carcinogenesis,[1] and that some of these events adversely affect prognosis.[2] Our group has characterised a large panel of colorectal adenocarcinomas for mutations in Kirsten-ras (K-ras), p53, and Adenomatous polyposis coli (APC), and we have now correlated these data with overall and disease specific survival.

106 patients in Tayside were recruited and their tumours characterised for mutations in K-ras, p53, and APC. Kaplan-Meier survival curves were constructed using overall survival and disease specific survival as the primary endpoints. Patient survival was analysed using the Log-rank test and Cox proportional hazards model.

Patients with K-ras mutations had significantly poorer survival than those patients without K-ras mutations ($p=0.003$). Multivariate analysis with Cox proportional hazards model confirmed that the presence of K-ras mutations in colorectal tumours predicted poor patient survival (hazard ratio 2.64 (95% CI 1.39 to 5.01)). When analysed according to disease stage, the prognostic effect of K-ras mutations was demonstrated in Duke's stage A and B patients ($p=0.003$) but not in Duke's C and D patients ($p=0.536$). P53 and APC mutations did not affect survival in this cohort of patients ($p=0.933$ and $p=0.808$, respectively).

Our data indicate that presence of K-ras mutations powerfully predict poor patient prognosis in early stage colorectal cancer. We suggest that colorectal cancers should be genotyped for K-ras mutations to identify patients with early stage tumours who may benefit from a more aggressive targeted treatment regimen.

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080 BOWEL CANCER PREVENTION: ASPIRIN INDUCES COX-2 INDEPENDENT ENDOTHELIAL CELL APOPTOSIS FACILITATING ANGIOGENESIS ARREST

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Background: NSAIDs such as aspirin have antineoplastic effects by unknown mechanisms, but are known to inhibit the cyclooxygenase (COX) enzymes, COX-1 and COX-2. COX-1, normally expressed, is thought to be responsible for gastric mucosa maintenance. COX-2, often not expressed in normal tissues, is inducible by inflammatory mediators and overexpressed in colorectal tumours. COX-2 selective inhibitors such as celecoxib were developed to reduce morbidity associated with non-selective COX inhibitors such as aspirin and are currently in polyp prevention clinical trials. Tumours secrete growth factors that cause nearby vessels to grow by angiogenesis, providing the tumour with nutrients. COX-2 expression may stimulate angiogenesis in vitro. We investigated the effect of aspirin and celecoxib on human microvascular endothelial cells (HMEC-1) and their effect on angiogenesis.

Materials and Methods: rtPCR was used to confirm that HMEC-1 express COX-1 and COX-2 genes. Endothelial cell viability, proliferation, and angiogenesis were assessed in response to a range of drug doses. The endothelial response was further investigated using TUNEL assays.

Results: Aspirin has a dose dependent effect on HMEC-1 viability, proliferation, and angiogenesis in vitro. It induces apoptosis at drug levels found within the normal therapeutic range. Celecoxib also has dose dependent effects on HMEC-1 viability, proliferation, and angiogenesis. However, concentrations far in excess of the therapeutic range were required to produce these responses.

Conclusion: Both aspirin and celecoxib caused dose dependent reduction in cell viability, proliferation, and angiogenesis. Celecoxib produced these effects at levels in excess of normal serum levels when it is no longer COX-2 selective. Aspirin induces apoptosis via a COX-2 independent mechanism which may facilitate angiogenesis arrest and play a critical role in limiting tumour growth.

081 THE NEW (6TH EDITION) TNM CLASSIFICATION OF COLORECTAL CANCER—A STAGE TOO FAR

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Background: The new 6th edition of the TNM staging classification of colorectal cancer changes the histological criteria for interpreting extramural tumour nodules. Previously these were called completely replaced lymph nodes if they measured >3 mm but the new rules state that they should have the ''form and smooth contour of a lymph node'', irrespective of size.

Aims: To assess pathologists' agreement in assessing the form and contour of extramural nodules and the impact of the new criteria on pathological staging.

Methods: Slides of 80 consecutive pT3 colorectal resection specimens were reviewed and the original pTNM staging by 5th edition criteria confirmed. Extramural tumour nodules ⩽3 mm diameter were photographed and categorised according to whether they had the form and smooth contour of a lymph node by 23 histopathologists of varying experience. Agreement was measured using kappa statistics. The 80 cases were then re-staged by the 6th edition criteria using the majority opinion for each nodule.

Results: Overall agreement on the form and contour of 40 sub-3 mm nodules was only fair (kappa=0.36) and unrelated to pathologists' experience. In 10/40 (23%) nodules more than one third of observers were discordant. Applying the 6th edition criteria upstaged 5/80 cases (6.25%) from N0 to N1 (Dukes B to Dukes C) and a further 4 from N1 to N2.

Conclusions: Changes to TNM staging in the 6th edition have replaced an objective criterion (size) with one that is subjective and not reproducible by pathologists. Application of the new TNM classification ''upstages'' up to 11% of T3 colorectal cancers. This has implications for patient treatment, clinical trials, and cancer intelligence.

Gastroduodenal free papers 082–091

082 NIGHT TIME HEARTBURN PREVALENCE AND IMPACT: A TELEPHONE SURVEY

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Introduction and Methods: Night time GORD symptoms are recognised as important but their impact may be underestimated. This cross sectional survey, based on a Gallup-style randomised telephone survey from scattered UK locations, ascertained the frequency, severity, patterns, and impact of night time heartburn in adult current sufferers, that is, those with heartburn in the previous month or those taking treatment.

Results: From 4142 subjects contacted 518 had current heartburn (females 62%), the chief symptoms comprising burning in the chest (76%) or throat (47%). 69% reported nocturnal symptoms, 90% day time symptoms. 40% of nocturnal sufferers had symptoms for 2–7 days/week compared with 63% of day time sufferers. 73% of nocturnal sufferers classed their symptoms moderate or severe. Sleep disturbance was reported by 82% of nocturnal heartburn sufferers, with 10% resorting to sleeping therapies as a result, and 42% reported an adverse effect on activity and function the following day, compared with 50% of day time only sufferers. 38% of those with moderate/severe nocturnal symptoms had not sought specific medical advice.

Conclusions: Night time heartburn affects the majority of sufferers but is likely to be under-reported and thus underestimated by clinicians in impact. It can substantially affect sleep and functioning the next day. Clinicians need to be aware of patients' night time symptoms and to tailor management accordingly, not least because of the association with complications.

083 ''GASTRIC EROSIONS''—REALITY OR MYTH

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Introduction: On endoscopic examination of the stomach small (<5 mm) white lesions are frequently seen. They are generally thought to be due to a breach in the mucosa and are usually referred to as ''erosions''. The aim of this study was to evaluate these lesions histologically.

Method: Consecutive patients undergoing endoscopy who were found to have gastric erosions were included in the study. Erosion was defined as a small (<5 mm) white lesion with the appearance of a superficial ulcer which could not be washed off. Two biopsies were obtained from across the erosion and two biopsies from the surrounding adjacent mucosa. The histology was then analysed by an experienced gastrointestinal pathologist. The results were analysed using Fisher's exact test.

Results: Of the 28 patients included in the study only five had a histologically demonstrable break in the mucosa from the erosion and in one patient from the adjacent mucosa. The histological appearance did not differ significantly between erosion and adjacent mucosa for the following characterstics: congestion (p=0.11), acute inflammation (p=0.36), chronic inflammation (p=0.53), and mucosal oedema (p=0.12). The only difference that just reached statistical significance was foveolar hyperplasia (p=0.05). The significance of this correlation is uncertain.

Conclusion: In the majority of the patients there was no demonstrable break in the mucosa from the biopsies of the erosion. The other histological changes were also largely identical to the surrounding mucosa. The term erosion would therefore appear to be inappropriate in most patients.

084 A COMPARISON OF GASTRITIS BETWEEN A UK AND A JAPANESE POPULATION

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Background and Aims: Cancer usually arises in a stomach with a corpus predominant gastritis that has undergone extensive atrophy and intestinal metaplasia. We would therefore expect to see an earlier and more severe gastritis with a corpus predominant pattern in a Japanese population together with a greater incidence of atrophy and intestinal metaplasia. The principal aim of this study was to compare gastritis in two age and symptom matched populations from the UK and Japan.

Methods: 126 patients were recruited from each centre (Leeds and Tokyo). There were 21 from each decennial from 20–80, all had epigastric discomfort as their principal symptom, and patients with peptic ulcer, cancer, and oesophagitis were excluded. Five biopsies were taken for assessment using the Updated Sydney System. Biopsies were also taken for *H pylori* culture and CagA/VacA status.

Results: 55/126 UK patients (44%) and 57/126 (45%) Japanese patients were histologically positive for *H pylori*. The pattern of gastritis was mainly corpus predominant in the Japanese (78% Japan *v* 36% UK) and antral predominant in the UK (64% UK *v* 22% Japan). Scores for atrophy and intestinal metaplasia (IM) were higher (Mann Whitney U (MWU) p<0.001) and occurred earlier (MWU p<0.001) in the Japanese population. Scores for inflammation were also greater, especially in the corpus (MWU p<0.001). Antral atrophy/IM (MWU p=0.018), corpus atrophy/IM (MWU p=0.01) and corpus inflammation (MWU p<0.001) all occurred earlier in the Japanese population. In Japan *H pylori* CagA/VacAS1M1 infection was associated with a greater degree of antral/corpus atrophy and IM (MWU p=0.029/0.036) and corpus inflammation (MWU p=0.001) compared to the UK.

Conclusion: Gastritis is more severe and progresses more rapidly to corpus predominant atrophy and intestinal metaplasia in a Japanese population despite a similar prevalence of *H pylori*.

085 PPIs, TTOs, AND NICE GUIDELINES: DETERMINING HOW TO REDUCE PRESCRIBING COSTS

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Introduction: Cornwall has the highest prescribing costs for PPIs in England and Wales. NICE has produced guidelines for cost effective PPI prescribing including treatment plans for dose and duration of use and use of most cost effective drugs. The county has a joint formulary (Primary and Secondary Care) with lansoprazole and rabeprazole chosen as first line agents on the basis of cost.

Method: A prospective audit of 131 consecutive discharge prescriptions containing PPIs to determine indication given, whether duration of use or plans for dose alteration stated, and which PPIs were prescribed.

Results: Of the patients identified, 64 (49%) were newly commenced on PPIs in hospital, mainly by non-GI physicians. The indication for commencing PPIs was not clear from either the discharge prescription or the case notes in 19 (30%). The commonest indications were for chest pain (without endoscopy: 25%) and reflux disease (28%). Other indications included gastritis/duodenitis (17%), peptic ulcer disease (11%), NSAID prophylaxis (9%), dyspepsia without endoscopy (5%), GI malignancy (5%), and hiatus hernia (4%). 46% were commenced on the second line agent omeprazole with more than half of these at a dose of 40 mg/day or higher. 1% were prescribed non-formulary PPIs. The indication for PPI therapy and the intended duration of use was stated in only 17% of discharge prescriptions and plans for alteration in dose in only 16%.

Conclusions: This audit demonstrated that PPIs were being initiated in secondary care without obvious indication. Communication with primary care regarding indication and intended duration of therapy and dose changes is extremely poor. Compliance with formulary choice to reduce

costs is also poor. There is widespread use of PPIs for non-licensed indications. We have demonstrated some of the reasons for high costs of PPI prescribing allowing plans to be made to reduce future expenditure (including individual treatment plans for patients plus pharmacy policing of PPIs prescribed).

086 AGEING AND *H PYLORI* INFECTION ALTER THE DIURNAL RHYTHM OF THE GASTRIC CYTOPROTECTIVE TREFOIL PROTEIN TFF2

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Introduction: TFF2 is a small cytoprotective protein synthesised by the gastric and duodenal mucosa. The concentration of TFF2 secreted into gastric juice has a circadian rhythm in young adults. The risk of peptic ulcer disease increases with age. We investigated whether age or *H pylori* infection alters the 24 h profile of TFF2 secretion.

Materials and Methods: Gastric juice was aspirated 2 hourly via a nasogastric tube from 23 healthy volunteers aged 16–82 years. *H pylori* status was determined by serology and C13 urea breath test. TFF2 was detected by quantitative Western transfer analysis.

Results: All volunteers had a marked circadian variation in TFF2 concentrations, with up to 100-fold higher concentrations reached at night compared to during the day. Infection with *H pylori* significantly reduced the fasted TFF2 concentration at 9 am ($p=0.009$). In the *H pylori* negative subgroup, older age was associated with a lower nocturnal peak of TFF2 ($r=-0.54$, $p=0.02$). In addition, the peak in TFF2 concentration occurred earlier in older volunteers ($r=-0.69$, $p=0.002$).

Conclusion: *H pylori* infection reduces the fasted concentration of TFF2 in gastric juice. This may contribute to the injurious effect of *H pylori* on the gastric mucosa. Older people have an earlier, lower peak of TFF2 in gastric juice. It may be that insufficient TFF2 is secreted at the wrong time in older people. This age related impairment in mucosal protective mechanisms potentially leaves the mucosa vulnerable to damaging agents.

087 THE *IL-8*-251 PROMOTER POLYMORPHISM IS ASSOCIATED WITH HIGH IL-8 PRODUCTION, SEVERE INFLAMMATION, AND INCREASED RISK OF PRE-MAILGNANT CHANGES IN *H PYLORI* POSITIVE SUBJECTS

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Background: Interleukin 8 (IL-8) is a key cytokine in the pathogenesis of *H pylori* related disease. It is a powerful chemotactic factor that induces many of the early inflammatory responses to *H pylori* infection. A recently described single nucleotide promoter polymorphism at position −251 (A/T) has been associated with viral bronchiolitis. There have been no reports on the functionality of this polymorphism and its relevance to *H pylori* related pathology.

Aim: To evaluate the effect of the *IL-8*-251 (A/T) polymorphism on IL-8 production in *H pylori* infected subjects and to study the contribution of this polymorphism to risk of pre-malignant changes in the stomach.

Subjects and Methods: Mucosal IL-8 levels were measured in 50 antral biopsies from *H pylori* infected subjects and correlated with *IL-8*-251 genotype. In addition, we assessed the effect of this polymorphism on premalignant gastric abnormalities in a case-control study comprising 52 infected subjects with hypochlorhydria/atrophy (HC/ATR), 66 infected subjects without these abnormalities, 52 *H pylori* negative subjects, and 100 population controls from Scotland.

Results: Carriage of the *IL-8*-251 A allele was associated with a very significant increase in mucosal IL-8 levels compared to the TT genotype (median for *IL-8*-251*A=195, range 41–660, compared to a median for TT genotype of 32, range 0–149, $p<0.003$). The A allele was also associated with significantly higher inflammatory scores. Carriage of the *IL-8*-251-A was associated with increased risk of HC/ATR (OR=2.2, 95% CI 1.3 to 7.6).

Conclusion: *IL-8*-251 A/T is a functional polymorphism and is very relevant to the pathogenesis of *H pylori* related disease. This polymorphism should be studied further as an important host genetic factor in GI disease.

088 *H PYLORI* INFECTION IN A CHINESE FISHING POPULATION: DOES HELMINTH INFECTION PROTECT AGAINST GASTRIC ATROPHY

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Introduction: Murine studies have shown infection with enteric helminths modulates gastric Th1 responses to *H pylori* and protects against gastric atrophy. There is no clinical data on the effects of helmimth co-infection on *H pylori* gastritis in humans. The aims of this study were to investigate *H pylori* infection and gastric atrophy in a population with a high prevalence of *Schistosoma japonicum*.

Methods: Demographic data and serum were obtained from 150 subjects from the Dongting Lake area in China. *S japonicum* infection was determined by faecal egg counts. *H pylori* and CagA status were assayed by IgG ELISA. IgG isotype (IgG 1~4) responses to *H pylori* and serum pepsinogen I and II were assayed by ELISA.

Results: The incidence of infection with *S japonicum* was 55.3% and *H pylori* 51.6% in the population. In the *H pylori* and *S japonicum* co-infected cohort (mean age 36.3) CagA positivity (52.3%) was significantly lower ($p<0.05$) than in those with only *H pylori* infection (75.8%) (mean age 37.7). There was no difference in the *H pylori* IgG1/2 ratio in the two groups, but the IgG1/3 was significantly higher ($p<0.05$) in co-infected subjects. The serum pepsinogen I/II ratio (a marker of gastric atrophy) in *H pylori* + subjects was significantly lower than in the non-infected group (mean (SEM) 7.57 (0.37) *v* 12.3 (0.31), $p<0.001$). In *S japonicum* + *H pylori* + subjects the pepsinogen I/II ratio (7.72 (0.52)) was significantly higher ($p<0.05$) than in those with *H pylori* only (6.22 (0.46)). The difference in pepsinogen I/II ratio between *S japonicum* + and *S japonicum* − *H pylori* + subjects was only evident in CagA-ve subjects (9.51 (0.84) *v* 6.06 (1.15), $p<0.03$) but not in the CagA+ subjects.

Conclusion: In subjects with both *H pylori* and *S japonicum* infection CagA seropositivity is reduced, which may reflect modulation of immune responses or strain selection. *S japonicum* co-infection was associated with a different IgG isotype response to *H pylori*, and less gastric atrophy but only in CagA negative subjects.

089 A FUNCTIONAL TOLL LIKE RECEPTOR 4 POLYMORPHISM INCREASES RISK OF GASTRIC CANCER

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Background: Host genetic factors are emerging as key determinants of clinical outcome of *H pylori* infection including gastric cancer (GC). Toll like receptor 4 (TLR4) is an important pattern recognition receptor that is key to eliciting an inflammatory response against bacterial lipopolysaccharide (LPS). We have recently shown that a functional missense mutation (Asp299Gly) in the fourth exon of the *TLR4* gene, which causes aberrant LPS handling, increases the risk of hypochlorhydria and premalignant changes in the stomach.

Aim: We examined whether the *TLR4* Asp299Gly polymorphism influences risk of gastric cancer (GC) in Caucasians.

Subjects and Methods: We used PCR-RFLP and 5′ nuclease assays to genotype the *TLR4* Asp299Gly polymorphism in a Polish population based case control study comprising 360 gastric cancer cases and 420 controls. Odds ratios and 95% confidence intervals (CI) were calculated and logistic regression was used to adjust for confounding variables.

Results: The frequency of the mutation in the control population was similar to other Caucasian populations (7%) and the alleles were in Hardy-Weinberg equilibrium. There was a significant association between carriage of the Asp299Gly mutation and increased risk of GC (adjusted OR=2.2, 95% CI 1.4 to 3.7). The increased risk applied equally to diffuse and intestinal type GC and was stronger for the non-cardia subsites. The risk was higher for *H pylori* positive cases.

Conclusions: Our results indicate that carriage of the *TLR4* Asp299Gly mutation increases risk of GC in this Caucasian population. We speculate that aberrant handling of LPS (of any origin) due to this mutation leads to an exaggerated inflammatory response that is characterised by severe gastritis, gastric atrophy, hypochlorhydria, and ultimately increased risk of GC. Our findings expand and strengthen the role of host genetic factors in the pathogenesis of *H pylori* induced GC.

090 FOVEOLIN IS ABUNDANTLY AND SPECIFICALLY EXPRESSED IN SUPERFICIAL GASTRIC EPITHELIUM, DOWN REGULATED IN GASTRIC CARCINOMA, AND SHOWS HIGH EVOLUTIONARY CONSERVATION

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Through previous large scale gene expression profiling we identified a transcript which was abundant in normal stomach and down regulated in gastric cancer. Genes expressed at similar levels included gastrin, MUC5, and pS2, which are important in gastric function. We aimed to characterise this candidate, foveolin, at mRNA, DNA, protein, and tissue levels. The gene was studied in human, mouse, rat, cow, and pig and was highly conserved across these species. By rapid amplification of cDNA ends, the mRNAs are all around 750 bp. The human, mouse, and rat genes contain six exons spanning 6 kb, located on chromosomes 2, 6, and 4, respectively. The full length proteins are 183–185 amino acids long (20 kDa), reducing to 163–165 amino acids (18 kDa) following cleavage of its signal peptide. These predictions have been confirmed by western blotting. Tagged foveolin yields abundant granular cytoplasmic staining with perinuclear accentuation, representing the Golgi apparatus, in keeping with secretion or expression on the extracellular surface. Gene expression in tissues was profiled extensively by northern blotting, in situ hybridisation, and immunohistochemistry. Foveolin was highly expressed in normal stomach, but absent from gastric carcinomas. Its location was in the superficial/foveolar gastric epithelium. Outwith the stomach, foveolin was found only in epithelia showing gastric metaplasia, for example Barrett's oesophagus, the ulcer associated cell lineage (UACL), and ovarian mucinous neoplasms. In conclusion, foveolin's abundance in and specificity to native or metaplastic gastric epithelium, down regulation in gastric carcinomas, and evolutionary conservation suggest that this gene is physiologically important in the stomach. Foveolin's function is unknown but a role in mucosal protection is postulated.

091 LONG TERM PRESCRIBING OF PROTON PUMP INHIBITORS IN PRIMARY CARE—A CROSS SECTIONAL SURVEY

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Introduction: PPIs constitute the single largest sector of primary care prescribing budget; £328 million was spent on PPIs in year 2000 and most of this is related to long term prescribing in primary care. One previous study had shown that 0.45% of the population are on long term PPIs.

Objectives: To ascertain the extent, variation, and determinants of long term PPI prescribing in a cross section of general practices in the UK.

Method: Data of patients over the age of 18 and on long term PPIs were collected from eight computerised practices situated in the northeast of England. The results were entered into excel spreadsheet for analysis. A long term prescription was defined as a repeat prescription for PPIs which had been commenced at least 6 months previously and was obtainable by the patient without a further consultation with the general practitioner, that is on a ''repeat'' basis.

Results: 648 of 46 933 patients were on long term PPIs, giving a mean rate of use of 1.38% (range 0.6–3.6%). The mean age of patients was 65.7 (range 18–97, SD 15.0), in females 68.3 (range 20–97, SD 14.3), and in males 62.3 (range 18–91, SD 15.2). The average endoscopy utilisation rate was 60% (55 to 79%); no upper GI procedures had been performed in 30% (20 to 45%) of patients. None of the practice characteristics (location, deprivation, size, male/female doctors, academic/research, PCT link, and GP with special interest) was clearly able to explain the variation in prescribing rates. The practice with the highest prescribing rate (3.6%) had the lowest endoscopy utilisation (55%) but the converse was not true.

Conclusions: This large cross sectional study has demonstrated a sixfold variation in long term prescribing rates of PPIs in primary care. Explanations for such variations are more likely to be found in the prescribing and referral behaviour of GPs and some of these decisions are complex and not fully explained by practice or GP characteristics.

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092 ACID IS NOT THE CAUSE OF RECURRENT SYMPTOMS FOLLOWING ANTI-REFLUX SURGERY

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Background: Anti-reflux surgery is effective in relieving symptoms in 85% of patients with gastro-oesophageal reflux disease (GORD). Surgery also resolves pathological reflux as measured by 24 hour oesophageal pH monitoring (24 h pH). Two recent studies have reported poor correlation between recurrent symptoms of GORD following anti-reflux surgery and findings on 24 h pH. We aimed to investigate this unexpected finding in our own patient population.

Methods: A database search of a regional oesophageal laboratory was performed using the term ''postoperative''.

Results: Following anti-reflux surgery, 107 patients with recurrent symptoms and 24 asymptomatic control patients underwent 24 h pH between Jan 1985 and Aug 2003. 111 patients had undergone Nissen fundoplication either as an open (90) or laparoscopic (21) procedure. Other anti-reflux operations performed included Angelchik (8), hiatus hernia repair (6), Toupet (2), and Roux-en-Y (2). In patients treated with Nissen fundoplication, the symptomatic and control groups were similar in preoperative total reflux (12.4% *v* 15.5%), age (47.8 *v* 52.7), sex, and symptoms. 59% (62/107) of patients with recurrent symptoms did not have pathological reflux on 24 h pH. Conversely, 25% (6/24) of asymptomatic patients had pathological reflux. Surgery decreased reflux in both the symptomatic group (12.4% to 6.4%) and the asymptomatic group (15.5% to 2.8%). This decrease was greater in the asymptomatic group, however, this difference was not statistically significant.

Conclusion: The majority of patients with recurrent symptoms following anti-reflux surgery do not have pathological reflux. This has important implications when considering long term proton pump inhibitors or revisional surgery and all patients with recurrent symptoms should have 24 h pH. There is increasing evidence for a role of anti-reflux surgery in the treatment of Barrett's oesophagus. For this subgroup of patients a repeat 24 h pH should be performed to confirm adequate control of reflux even in patients who are asymptomatic.

093 RISK FACTORS FOR GASTRO-OESOPHAGEAL REFLUX SYMPTOMS: A COMMUNITY STUDY

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Gastro-oesophageal reflux disease (GORD) is very common, associated with substantial therapeutic costs, and is a major risk factor for oesophageal adenocarcinoma. However, its aetiology remains poorly understood. We have examined the prevalence of GORD symptoms and potential risk factors in the local community.

Methods: A validated questionnaire was sent to 4000 subjects over the age of 18, stratified by age, gender, and ethnicity to be representative of the Sandwell population at the 2001 Census. GORD was defined as at least weekly symptoms of heartburn or acid regurgitation.

Results: 2231 subjects responded (59%). 691 (18%) refused to participate and 7 were incomplete. 1533 (41%) were evaluable (637 males, mean age 50 SD16 (20–80) years). Non responders were more likely to be male and younger ($p<0.0001$). GORD prevalence was 21 (95 CI 19 to 23)%. Univariate analysis suggested smoking OR 1.74 (95 CI 1.14 to 1.87), excess alcohol intake 2.87 (1.59 to 5.19), irritable bowel syndrome (IBS) 4.21 (3.17 to 5.58), log body mass index (BMI) 23.16 (4.74 to 113.13), a family history of upper GI disease 2.58 (1.97 to 3.37), anticholinergic drug use 3.79 (2.16 to 6.66), (all $p<0.0001$), weight gain as an adult 1.01 (1.00 to 1.02, $p<0.01$), antidepressants 2.14 (1.21 to 3.80, $p<0.01$), inhaled bronchodilators 2.61 (1.34 to 5.09, $p=0.005$), South Asian origin 1.61 (1.08 to 2.39, $p=0.02$), and manual work 1.57 (1.01 to 2.44, $p<0.05$) were associated with GORD. Any educational attainment was negatively associated with GORD (0.69 (0.53–0.90, $p<0.01$)). Multivariate forward stepwise logistic regression analysis confirmed BMI, a family history of upper GI disease, IBS, South Asian origin (all $p<0.0001$), smoking ($p=0.004$), excess alcohol intake ($p=0.001$), no educational attainment ($p=0.006$), and anticholinergic drug use ($p=0.006$) were independently associated with GORD.

Conclusions: Increasing BMI, a family history of upper GI disease, IBS, South Asian origin, smoking, excess alcohol intake, no educational attainment, and anticholinergic drug use are independently associated with GORD symptoms in community subjects.

094 NOCTURNAL PATTERNS OF SUPINE REFLUX

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Aim: A recent study[1] concluded that supine reflux occurs mainly in the early part of the night time period. There was a strong association between supine reflux and retiring within 2 hours of a meal. We aimed to test this hypothesis in more detail in a larger cohort of patients.

Methods: 352 consecutive pH studies between January 2003 and July 2003 were analysed. Abnormal supine and upright reflux were defined as >3.45% and >8.15% time pH <4, respectively. For patients with abnormal supine reflux, the recumbent period was divided into quarters (Q1–Q4) and the reflux time (%), number of refluxes (n), and length of the longest reflux in minutes (l) in each period was calculated. Time between evening meal and retiring was also determined.

Results: 92 (62 M mean age 50.2 years) patients had abnormal supine reflux, which was maximal in the earlier quarters of the night.

Subgroup analysis showed a similar pattern in 55 patients with features of both supine and upright reflux (Q4% *v* Q1%; $p<0.001$), but not in 37 patients with pure supine reflux (Q4% *v* Q1%; $p=0.147$). In all 92 patients median time between evening meal and retiring was 3 hrs 26 min, and not significantly different from a control group of 44 pure upright reflux patients ($p=0.31$). Only 18 patients retired within 2 hours of a meal, however these patients did have more supine reflux than those that retired after more than 2 hours ($p=0.012$).

Conclusion: Reflux in mixed supine and upright reflux patients occurs maximally in the early part of the night, and this may be important for the timing of acid suppressive therapy. Patients with reflux confined to the supine period, however, appear to reflux equally throughout the recumbent period. Supine reflux is not fully explained as a post-prandial phenomenon, however, patients that do have abnormal supine reflux should avoid going to bed within 2 hours of their evening meal.

1. Night-time Reflux: Is it an early or late event? Hila A, *et al*. AGA: M2089, 2003.

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	Q1 median	Q2 median	Q3 median	Q4 median	p (Q1 *v* Q4)
%	18.9	11.8	4.9	1.9	p<0.001
L	12.5	11.5	3.0	1.0	p<0.001
N	6.5	5.0	5.5	3.0	p=0.005

095 THE EFFECT OF LIFESTYLE MEASURES ON THE SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISEASE (GORD)

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Introduction: In the treatment of GORD, advice on lifestyle is often given, but its effects have not been well evaluated. We aimed to assess the impact of lifestyle measures on symptoms of GORD.

Methods: This was a randomised, controlled, single blind trial. Patients were recruited if their predominant symptom was either heartburn or regurgitation. Patients with severe oesophagitis were excluded. They were randomised into 1) postural group (receiving detailed advice re raising the head of the bed and not eating/drinking for 3 hours prior to going to bed), or 2) control group (receiving a patient information pamphlet). All medications were left unchanged. Symptom scores and quality of life scores (QOLRAD) were assessed at weeks 0 and 2 (assessor unaware of which group the patient was in).

Results: 47 patients were recruited (31 male, 16 female).

Conclusion: Reflux symptoms were significantly improved (both patient reported and researcher assessed) at 2 weeks in the postural compared to the control group, by both intention to treat and per-protocol analysis. Changes in the QOLRAD score numerically improved in the postural group, but did not reach statistical significance. Our data suggest that lifestyle measures reduce symptoms in mild GORD.

096 ACID PERFUSION TEST: A USEFUL TEST FOR EVALUATING OESOPHAGEAL ACID SENSITIVITY

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Background: The acid perfusion test (APT) has been used to investigate the reproduction of gastro-oesophageal reflux symptoms, but has never been fully validated. For patients undergoing 24 h oesophageal pH monitoring, the symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP) define the association between reflux episodes and symptom perception; the SAP is the only method that controls for chance association. The aim of the present study was to validate the APT by comparing SI, SSI, and SAP in APT+ve *v* APT–ve patients.

Methods: Between Jan 2002 and Sept 2003 our laboratory performed both successful APT and 24 h oesophageal pH monitoring on 272 patients. 126 (72 Males, mean age 44.9) were APT+ve and 146 (68 Males, mean age 48.3) were APT-ve. For each of these patients SI, SSI, and SAP were calculated from their 24 h oesophageal pH record. For those who reported no symptoms all three indices were recorded as being 0. SI >50%, SSI >10%, and SAP>95% are defined as positive.

Results: Median values for SI, SSI, and SAP are compared in the table 78/126 APT+ve *v* 32/146 APT-ve patients had a positive SI ($\chi^2=44.9$, $p<0.0001$), 28/126 APT+ve *v* 8/146 APT-ve patients had a positive SSI ($\chi^2=16.5$, $p<0.001$), and 48/126 APT+ve *v* 20/146 APT-ve patients had a positive SAP ($\chi^2=21.5$, $p<0.001$). The negative predictive value of the APT using SAP as the gold standard was 86%. 24/126 (17%) APT +ve patients reported no symptoms on 24 h oesophageal pH monitoring.

Conclusion: Values for SI, SSI, and SAP are significantly higher in patients who have a positive APT, and APT+ve patients are more likely to be positive for all three of these indices. Patients who have a negative APT are highly unlikely to have symptoms caused by acid reflux. APT may also be useful in detecting acid sensitivity in those who do not report symptoms on 24 h oesophageal pH monitoring.

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	APT+ve	APT-ve	Significance (Mann-Whitney U)
SI	66.7%	0%	p<0.001
SSI	3.75%	0%	p<0.001
SAP	83.3%	7.55%	p<0.001

097 LOW INCIDENCE OF CANCER IN PATIENTS WITH HIGH GRADE DYSPLASIA IN BARRETT'S OESOPHAGUS

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		Per-protocol (n=37)			Intention to treat (n=47)		
		Postural	Control	p	Postural	Control	p
Patient reported change in symptoms QOLRAD score	Improved	9	1	0.002*	11	5	0.037*
	Same/worsened	8	19	0.002*	11	20	0.037*
	Improved	14	11	0.09	18	14	0.069
	Same/worsened	3	9	0.09	4	11	0.069
Researcher assessed change in symptoms	Improved	12	5	0.009*	15	8	0.02*
	Same/worsened	5	15	0.009*	7	17	0.02*

*p<0.05. Fisher's exact test used.

Background: Previous studies suggest that when high grade dysplasia (HGD) is diagnosed within Barrett's oesophagus, up to 50% of patients have invasive cancer so should be offered surgery. We documented the true prevalence of cancer in patients referred to the National Medical Laser Centre to enter trials of photodynamic therapy (PDT).

Patients and Methods: All patients who were referred for assessment of dysplasia from January 1998 to September 2003 were included in this study. Most were not considered to be surgically fit. In 91% (n=67) of cases our specialist GI pathologist reviewed slides from the referring hospital. A further UCLH pathologist examined the slides if there was disagreement. All patients were then assessed at UCLH by endoscopy, quadrantric jumbo biopsies every 2 cm and endoscopic ultrasound.

Results: 86 patients were referred (74 HGD; 12 LGD). Referral rates increased by 30% per year. Median follow up is now more than 2 years. Agreement between pathologists on the original biopsies was high for HGD (64/67 patients, 95%). The other 3 were cancer (n=1) and no dysplasia (n=2). Further assessment at UCLH demonstrated that 7 of these 64 patients (11%) with HGD actually had invasive cancer. The other 57 (89%) had HGD. Only 2 of these were found to have cancer during the next year (although most had been treated with PDT in the meantime). Four of the 7 patients whose original slides were not sent to us to re-examine had invasive cancer at our assessment. Overall 11/74 (15%) referred as HGD had invasive cancer after our assessment. Of 12 patients referred with LGD, we only agreed with the diagnosis in 5 (33%). The others had no dysplasia except 1 who had invasive cancer.

Discussion: This study shows good agreement in the diagnosis of HGD among pathologists and demonstrates the huge interobserver variation in the diagnosis of low grade dysplasia in BE. Cancer was only detected in 13 of 74 cases of HGD (18%) at presentation to us or during the following year, a lower figure than has previously been reported. This could justify including surgically fit patients in PDT trials.

098 A RETROSPECTIVE CASE CONTROL STUDY TO DETERMINE THE RISK OF BARRETT'S OESOPHAGUS ACCORDING TO ETHNIC ORIGIN

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Background: Barrett's oesophagus is thought to be a disease that occurs predominantly in whites compared with other ethnic groups. A BSG report, however, found surprisingly little data in this area and identified only two papers with a total of 56 cases of Barrett's oesophagus evaluating racial differences.

Aims: To conduct a retrospective case control study to determine the incidence of Barrett's oesophagus in Asian and white patients.

Methods: All patients who had undergone upper gastrointestinal endoscopy at two centres in Birmingham and Bradford were evaluated. Endoscopic records from January 2000 to January 2003 period were retrieved from hospital databases. Data on ethnicity, age, and sex were collected, along with presence or absence of Barrett's oesophagus at endoscopy (defined as at least 3 cm of columnar lined oesophagus +/− intestinal metaplasia). The length of the Barrett's segment, presence of intestinal metaplasia, and evidence of dysplasia (and severity) or malignancy was also recorded.

Results: 20 455 patients were endoscoped. Barrett's oesophagus was more common in white (690/15063 (4.6%)) compared with Asian (45/5297 (0.8%)) patients (odds ratio (OR) =5.6; 95% CI 4.1 to 7.6). Patients with Barrett's oesophagus were more likely to be male (OR=2.2; 95% CI=1.9 to 2.5) and older than 55 years (OR=2.8; 95% CI=2.3 to 3.3). White race remained a strong risk factor for Barrett's oesophagus in a logistic regression model adjusting for age and sex (OR=4.5; 95% CI=3.3 to 6.1). There were 18 cases of oesophageal adenocarcinoma in patients with Barrett's oesophagus and all were white.

Conclusions: White race is a strong risk factor for Barrett's oesophagus although the reasons for this remain unclear.

099 CELL CYCLE PHASE DISTRIBUTION IN NEOPLASTIC PROGRESSION OF BARRETT'S OESOPHAGUS

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Introduction: It has been demonstrated that there is an increased proliferation index as the Barrett's oesophagus (BE) mucosa progresses through the metaplasia–dysplasia–adenocarcinoma sequence. Understanding of the cell cycle phase distribution in BE could shed light on the basic abnormalities leading to uncontrolled proliferation and cancer progression.

Aim: To determine whether the increased proliferation associated with progression of Barrett's oesophagus could be attributed to abnormalities in cell cycle phase.

Methods: Archival material (35 BE, 26 BE with low grade dysplasia (LGD), 11 BE with high grade dysplasia (HGD), 16 invasive adenocarcinoma (AC), 10 duodenum (D2), and 20 gastric antrum) was immunostained for proliferation markers (mini-chromosome maintenance protein 2 (Mcm 2) and Ki-67) and for cell cycle phase markers (cyclin D1 for late G1 phase, cyclin A, for S, G2 and M phases, cytoplasmic cyclin B1 for G2 phase and phosphorylated histone H3 (pH3) for M phase).

Results: The proliferation levels of non-dysplastic BE were shown to be similar to gastric antrum and duodenum with either Mcm 2 or Ki-67 antibodies. Proliferation increased as BE progressed to dysplasia and cancer (Mcm 2, $p<0.0001$; Ki-67, $p<0.001$). There was a correlation between Mcm 2, Ki-67, cyclin A, and cyclin B1 expression levels and the degree of dysplasia ($p<0.001$). The expression levels of pH3 increased with progression but statistical significance was not reached. No clear trend was seen in cyclin D1 expression. When expressed as a percentage of total Mcm 2, the expression levels of cyclin D1, cyclin A, cyclin B1, and pH3 were constant as BE progresses to cancer.

Conclusions: Contrary to popular belief, non-dysplastic BE was not hyperproliferative. Proliferation increased during progression to dysplasia and cancer as expected. However, the distribution of the cell cycle phases is conserved throughout the metaplasia–dysplasia–carcinoma sequence. Therefore, it is likely that the increase in proliferation as BE progresses to cancer is due to abnormal cell cycle entry.

100 SUPPRESSION OF COX-2 EXPRESSION IN HUMAN ADENOCARCINOMA CELLS (OE33) CULTURED WITH EICOSAPENTAENOIC ACID (EPA)

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Background: Oesophageal adenocarcinoma initiation and progression is associated with elevated levels of cyclo-oygenase 2 (COX-2) expression. The use of synthetic COX-2 inhibitors as chemo-preventative therapy is limited by side effects. There is epidemiological and experimental evidence to suggest that certain n-3 fatty acids have a protective effect, which may be mediated through inhibition of COX-2 expression.

Aim: To investigate the suppressive effect of EPA on COX-2 gene expression in a human oesophageal adenocarcinoma cell line (OE33).

Method: A comparative study was made using physiological concentrations of n-3 fatty acids, EPA, and docosahexaenoic acid (DHA), n-9 fatty acid, oleic acid, and selective COX-2 inhibitors to treat OE33 cells. After 48 hours under standard conditions, the cells were harvested and RNA extracted for measurement of COX-2 using Taqman real time PCR.

Results: Treatment with EPA (250 uM) decreased COX-2 mRNA expression from 0.85 ug/ul to 0.18 ug/ul, 21% of that expressed by control cells. DHA (250 uM) reduced COX-2 mRNA expression from 1 ug/ul to 0.55 ug/ul (55%). Oleic acid (500 uM), an n-9 mono-unsaturated fatty acid, did not affect COX-2 expression while COX-2 inhibitors, niflumic acid, NS398, and nimesulide also reduced COX-2 expression to 60% of the control value.

Conclusion: EPA at a physiological dose has a significant suppressive effect on COX-2 expression at the transcriptional level compared with other long chain fatty acids and synthetic COX-2 inhibitors. This suggests that EPA may be a viable alternative to NSAIDs as chemopreventative therapy.

101 SURVEILLANCE IMPLICATIONS FOR OESOPHAGEAL ADENOCARCINOMA USING LAGERGREN CRITERIA FOR RISK

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Background and Aims: Severe and longstanding reflux is a significant risk factor (up to 40 times) for oesophageal adenocarcinoma (OA). This risk may be independent of the presence of Barrett's oesophagus (Lagergren, *et al. N Engl J Med* 1999;**340**:825–31).We wished to assess what proportion of outpatient referrals for OGD are at high risk for OA according to the Lagergren criteria and the implications for screening this group for continued surveillance.

Patients and Method: We assessed 100 consecutive patients presenting for outpatient endoscopy for any indication with a questionnaire which was closely based on the Lagergen paper and allowed us to calculate the reflux score (Heartburn only = 1 point; regurgitation only = 1; heartburn and regurgitation = 1.5; nightly symptoms no = 0, yes = 2; frequency of symptoms once per week = 0, 2–6 = 1, 7–15 = 2, >15 = 3; Max 6.5); symptom duration; and consequent odds ratio for OA.

Results: 92 questionnaires were available for analysis. Of all patients attending, 28.3% had a reflux score ⩾4.5, Lagergren odds ratio for oesophageal adenocarcinoma (LOR) 20.0, 3.3% had ⩾20 years of symptoms, LOR 16.4, 1.1% had both, LOR 43.5. Of those with reflux as their primary indication for referral (33/92), the results were 48.5%, 6.1%, 6.1%, respectively. Of the group referred for reflux with a reflux score ⩾4.5, 1 patient had Barrett's oesophagus, 3 had short segment Barrett's (<3 cm columnar mucosa), only one of which was confirmed histologically. Screening this group in our practice (3000 OGD/year) for intestinal metaplasia/dysplasia would require 978 biopsies (2/patient, 1 case of Barrett's excluded) leading to 73 patients for surveillance, assuming 15% show intestinal metaplasia (Nandurkar S, *et al. Am J Gastrenterol* 1999;**94**:30–40)

Conclusion: Half those attending for OGD for reflux symptoms have a Lagergren reflux score consistent with an odds ratio 20 times that of a control population for oesophageal adenocarcinoma at 5 years. Few have Barrett's oesophagus, the only endoscopically visible risk factor for adenocarcinoma. Screening this group would be very resource intensive but would require limited ongoing surveillance.

102 BARRETT'S OESOPHAGUS: OESOPHAGEAL ADENOCARCINOMA INCIDENCE AND RISK FACTORS

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Background: Barrett's oesophagus (BO) is associated with the development of oesophageal adenocarcinoma (OA). However, recent evidence suggests many existing studies have been too small and overestimate the risk of OA. We have the largest follow up series of BO in England and have examined the incidence of OA and risk factors for its development.

Methods: Retrospective analysis of patients undergoing endoscopic surveillance for BO at Sandwell, City, and Northern General Hospitals between 1990 and 2002. Endoscopy, histopathology, and clinical coding records were reviewed for cases of BO. Inclusion criteria: at least two endoscopies 12 months apart without high grade dysplasia or OA; red ''gastric-type'' mucosa above the proximal margin of the gastric folds; intestinal metaplasia on biopsy.

Results: 455 patients met the inclusion criteria (267 male, median age 53 (31–97) years) and were surveyed for 2004 patient years (median 3 (1–18) years). There were 14 cases of OA, that is 1 per 143 patient years of follow up (annual risk 0.70%). The risk in males was 0.93% (1 per 107 years) and in females 0.25% (1 per 400 years of patient follow up) ($p<0.05$). OA was associated with a previous benign ulcer in the BO segment ($p<0.05$) but not the BO segment length.

Conclusion: In this the largest series of patients with BO to date, male patients and patients with a history of a benign ulcer in their BO segment were at particular risk of oesophageal adenocarcinoma. BO surveillance should be targeted at high risk groups.

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	Male	Benign ulcer	Median length (cm)
Adenocarcinoma	12/14(86%)*	4/14(28%)*	7(1–13)
No adenocarcinoma	267/441(60%)	39/441(9%)	6(1–15)

*$p<0.05$ versus no adenocarcinoma.

103 OUTCOME PREDICTION FOLLOWING NEOADJUVANT ECF CHEMOTHERAPY FOR OESOPHAGO-GASTRIC CANCER

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Introduction: Neoadjuvant chemotherapy is increasingly being used to downstage locally advanced oesophago-gastric cancer. Predicting response to treatment is important in order to target surgery to those individuals who would derive the maximum benefit. The aim of this study was to assess whether radiological or symptomatic (swallowing, weight, and performance status) parameters could aid surgical decision making.

Methods: All patients with potentially operable carcinoma of the lower oesophagus or cardia in AJCC stages II-IV treated with neoadjuvant ECF (or ECF-like) chemotherapy between January 2000 and January 2003 were identified from oncology databases and their case notes retrospectively reviewed.

Results: 78 patients (M:F ratio, 6.8:1; median age, 62.2 years; range, 44.1–78.0 years; 39.7% initially operable, 60.3% initially inoperable) underwent a median of 3 cycles (range, 1–7) of neoadjuvant chemotherapy. Overall median survival was 384 days with 61.5% of patients proceeding to surgery. During chemotherapy, swallowing, performance status, and weight (>5% body weight) improved in 75.7%, 54.3%, and 31.9% of patients, respectively. Radiological changes (based primarily upon computerised tomography) were assessed according to WHO criteria: complete response (5.5%), partial response (28.8%), stable disease (49.3%), and progressive disease (16.4%). Univariate analysis (using the log rank test) suggested that each of these parameters were significant determinants of overall survival ($p<0.05$). Multivariate analysis (using Cox's proportional hazards model) suggested that only radiological assessment was significantly associated with overall survival ($p=0.01$).

Conclusions: Both biological and radiological responses to neoadjuvant ECF chemotherapy should play an important role in surgical decision making. These parameters should be carefully measured and assessed in future prospective trials.

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104 ALTERED AUTONOMIC CARDIOVASCULAR RESPONSES IN WOMEN WITH IRRITABLE BOWEL SYNDROME (IBS)

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Aims: Altered autonomic function has been reported both in IBS and in anxiety and depression disorders and may contribute to abnormalities of gastrointestinal motility and visceral hypersensitivity. We hypothesised that alterations in autonomic function may reflect increased central nervous system arousal associated with anxiety and depression as assessed using Hospital Anxiety and Depression (HAD) rating scale.

Method: Patients recently referred from primary care to hospital gastroenterology clinics were recruited prospectively. The diagnosis of IBS was based on the Rome II criteria and the autonomic responses to a variety of cardiovascular stimuli were studied in a controlled manner. Heart rate variability (HRV) was determined in 30 IBS patients and 30 age matched healthy controls. The ratio of low frequency to high frequency variability domains (LF:HF) was used to represent sympathovagal cardiac influence. The effects of sustained isometric handgrip exercise and orthostatic testing (sympathetic stimuli) were assessed. The expiratory:inspiratory R-R interval (E:I) ratio during deep breathing represented parasympathetic cardiac effects. The HAD ratings were obtained immediately prior to autonomic function testing.

Results: Resting heart rate, blood pressure, and LF:HF ratio were similar in IBS patients and healthy controls. IBS patients had a greater LF:HF response to handgrip exercise (316 (SD 91) % *v* 107 (46) %; $p<0.05$) and orthostatic testing (648 (128) % *v* 330 (95) %; $p<0.05$). The E:I ratio during deep breathing was significantly lower in IBS patients (1.47 (0.07) *v* 1.20 (0.06); $p<0.01$). No correlation was found between cardiovascular autonomic responses and HAD ratings.

Conclusion: Patients with IBS demonstrate decreased parasympathetic and increased sympathetic responses to cardiovascular stimulation, which did not correlate with anxiety or depression ratings. Alhough alterations in autonomic function could play a role in IBS, further research is required to identify the underlying mechanisms at play.

105 SENSITISATION *V* HYPERVIGILANCE: IDENTIFYING THE NEUROPHYSIOLOGICAL MECHANISMS OF VISCERAL HYPERSENSITIVITY IN NON-CARDIAC CHEST PAIN

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Background: One of the major problems encountered by researchers studying the aetiology of non-cardiac chest pain (NCCP) is the heterogeneity of the group. While visceral hypersensitivity (VH) is thought to be important in the generation of symptoms in NCCP, conventional physiological assessments do not allow us to objectively investigate or differentiate between the potential neurophysiological mechanisms that may cause it. Therefore, the aim of this study was to explore the neurophysiological basis for VH in NCCP.

Methods: We studied 12 healthy control subjects (6 female, 21–46 years) and 31 patients with NCCP (24 female, 20–70 years). Oesophageal evoked potentials (OEP) were recorded following electrical stimulation (ES) of the distal oesophagus, at a frequency of 0.2 Hz and an intensity that was 75% between sensory (ST) and pain threshold (PT). An average of 200 stimuli were recorded.

Results: 6 patients did not report pain at the maximum intensity of 100 mA and were therefore excluded from further analysis. The remaining 25 NCCP patients had significantly lower PT when compared to normal (47.1 mA (15.5) *v* 72 mA (18.3), p=0.002). OEP data revealed that the NCCP group could be divided into three distinct subgroups; 1, normal PT with normal OEP (n=6); 2, reduced PT with potentiated early and late OEP components (n=9); 3, reduced PT with delayed early OEP components but potentiated late OEP components (n=10).

Conclusions: The potentiation of OEP components in group 2 patients indicates enhanced oesophageal afferent transmission, similar to that seen following the induction of experimental oesophageal sensitisation (Sarkar *et al* 2001). The late components of OEP relate to the cognitive and emotional processing of oesophageal sensation, thus the profile demonstrated by group 3 patients implies normal afferent transmission to the cortex but secondary processing of this information is heightened, most likely due to psychological factors such as hypervigilance. This is the first study to objectively differentiate between the specific mechanisms of VH in individual NCCP patients. This approach will allow future treatment strategies to be specifically targeted with great benefits to both patients well being and healthcare utilisation.

106 DIFFERENTIAL EFFECTS OF PLEASANT AND AVERSIVE TASTE STIMULI ON HUMAN CORTICAL SWALLOWING PATHWAYS

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Background and Aims: Human swallowing is a multidimensional experience, involving the integration of sensorimotor information with more complex behaviours such as taste. However, the interaction between taste and the cortical control of human swallowing remains unknown. The aim of this study was to assess the effects of differing taste experiences on human cortical swallowing pathways.

Methods: In healthy adult volunteers (n=8, 7 male, mean age 29 years) we performed a 10 min liquid swallowing task using three (previously titrated) taste solutions; sterile water (neutral), 10% glucose (sweet/pleasant), and 0.5 mM quinine hydrochloride (bitter/aversive). Solutions were randomised to separate studies at least 24 hours apart. Transcranial magnetic stimulation (TMS) was performed over swallowing motor cortex before and up to 1 hour after each swallow task, and cortico-pharyngeal motor responses were recorded from a swallowed intraluminal catheter. Cortico-pharyngeal responses for each condition were then compared using repeated measures ANOVA.

Results: Following neutral water, cortico-pharyngeal responses were increased but only in the period immediately after swallowing (% change from baseline = 36 (SD 15) %, $p<0.04$), returning to baseline by 30 min. By comparison, following aversive quinine, responses were increased both immediately and throughout the 60 minutes post-intervention period (maximum % change from baseline = 48 (11) %, $p<0.01$). However, following pleasant glucose, no changes in response were observed.

Conclusions: Cortical swallowing pathways are modulated in a differential manner by pleasant and aversive tasting stimuli. In comparison to neutral stimuli, aversive tastes enhance the cortical swallowing responses whereas pleasant tastes suppress these pathways. This finding may help guide the use of taste stimuli as a method for rehabilitating swallowing problems after cerebral injury.

107 ABDOMINAL BLOATING IN THE ABSENCE OF PHYSICAL DISTENSION IS RELATED TO INCREASED VISCERAL SENSITIVITY

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Patients with irritable bowel syndrome (IBS) who experience the symptom of bloating can be sub-divided according to whether there is associated visible abdominal distension or not.[1] Although bloating might well be the symptomatic manifestation of physical abdominal distension in some patients, it is less clear why others experience bloating in the absence of such distension. The aim of this study was to assess whether rectal sensitivity differs between these two groups of IBS patients.

Methods: Abdominal girth was recorded for 24 hours using the recently validated objective technique of Ambulatory Abdominal Inductance Plethysmography[2] in 37 IBS (Rome II) patients aged 18–73 years (33 female) and 20 healthy volunteers aged 18–67 years (20 female). All patients were asked to grade the severity of their bloating on a scale of 0–3. Within 7 days rectal sensitivity was assessed using a barostat technique, in which pain thresholds were determined using the ascending methods of limits followed by tracking.

Results: In the healthy volunteers the mean change in girth from the beginning to end of the day was −0.2 cm (95% CI −2.7 to 2.3 cm). Using this 95% reference range, 21 (57%) patients distended significantly more than healthy volunteers, while the rest fell either within (12 patients) or below (4 patients) these limits. Those patients who did not exhibit physical abdominal distension had significantly lower rectal pain thresholds (25.5 mmHg (19.6 to 31.4 mmHg) than those who distended (34.0 mmHg (28.3 to 40.0 mmHg), (p=0.04). Furthermore, sensory thresholds in the non-distending patients were comparable with our departmental lower 2.5th percentile limit for healthy volunteers (31.3 mmHg (24.5 to 38.0 mmHg); mean (95% CI)) indicating that they were rectally hypersensitive. Interestingly, the severity of bloating was similar in both groups (distending: 2.2 (1.9 to 2.5), non distending 2.1 (1.5, 2.6)).

Conclusion: These data suggest that patients who experience the symptom of bloating in the absence of visible distension may do so because of increased visceral sensitivity to gastrointestinal events.

1. **Chang**, *et al. Am J Gastroenterol* 2001.
2. **Lewis**, *et al. Gut* 2001.

108 BACTERIAL ENTEROTOXINS STIMULATE RELEASE OF THE NEUROTRANSMITTER [^{3}H] NORADRENALINE FROM NEURONALLY DIFFERENTIATED PC12 CELLS

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The bacterial enterotoxins cholera toxin (CT), *Escherichia coli* heat labile (LT) and heat stable (ST) toxins are thought in part to mediate intestinal secretion through an enteric reflex arc. These toxins may activate a secretory response by interacting directly with enteric nerves. Previously we have shown that CT and LT induce neurite outgrowth in PC12 cells and enhance the neuronal differentiation effects of nerve growth factor (NGF). A direct functional effect of these enterotoxins was investigated by measuring neurotransmitter release; [^{3}H] noradrenaline (NA) loaded PC12 cells were used as a model system.

Method: NGF differentiated PC12 cells grown on rat-tail collagen coated coverslips were loaded with 2 μCi [^{3}H] NA/ml for 1 hour at 37°C. Following triple washings, PC12 cells were incubated for 15 min at 37°C in release buffer alone and in the presence of either CT, LT, ST (0.001–1.0 μg/ml), or ouabain (0.3 mM) acting as a positive control. [^{3}H] NA was measured in release buffer and cell lysates by liquid scintillation spectrometry; [^{3}H] NA secretion is expressed as a percentage of total [^{3}H] NA per condition.

Results: Mean percentage release of [^{3}H] NA from [^{3}H] NA loaded PC12 cells after 15 min incubation under basal conditions was 21.8% (9.1). Mean percentage release of [^{3}H] NA in the presence of ouabain was 52.3% (3.65). Mean percentage release of [^{3}H] NA from [^{3}H] NA loaded PC12 cells after 15 min incubation with CT, LT, and ST was 58.3% (4.89), 55.3% (0.89), 41.7% (7.64), respectively ($p<0.01$). There was no significant dose dependent effect.

Discussion: CT, LT, and ST all stimulate [^{3}H] NA secretion from PC12 cells. These observations support the hypothesis that bacterial enterotoxins are able to stimulate nerves directly. It is now known that enteric nerves reach the intestinal mucosal surface and it is possible that CT, LT, and ST stimulate a secretory neuronal reflex via direct neuronal stimulation.

109 EXPRESSION OF CANNABINOID CB-1 RECEPTORS BY VAGAL AFFERENT NEURONES AND INHIBITION BY CHOLECYSTOKININ (CCK)

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Background and Aims: Both inhibitory (satiety) and stimulatory (orexigenic) factors from the gastrointestinal tract regulate food intake. In the case of the satiety peptide CCK these effects are mediated via vagal afferent nerve fibres. Since endogenous cannabinoid (CB)1 receptors are associated with stimulation of appetite, we asked whether vagal afferent neurones that express CCK-1 receptors also express CB1 receptors.

Methods: Immunohistochemistry using specific CB1 antibodies, in situ hybridisation, RT-PCR, and retrograde tracing from the stomach using True Blue, were applied to the characterisation of vagal afferent neurones in rats fed ad libitum, fasted for 24–48 hr or fasted and refed.

Results: In rats fed ad libitum, there was a barely detectable product corresponding to CB1 in RT-PCR of nodose ganglia. In contrast, in fasted rats a strong signal was identified. Similarly using immunohistochemistry and in situ hybridisation, CB1 expression in nodose ganglia was barely detectable in rats fed ad libitum but was increased markedly in fasting. Retrograde tracing indicated that neurones expressing CB1 receptors projected to the stomach and duodenum and co-localisation studies indicated that they also expressed CCK-1 receptors. After refeeding of fasted rats there was a rapid loss of CB1 receptors identified by immunohistochemistry and in situ hybridisation, which was blocked by administration of the CCK-1 receptor antagonist lorglumide. CB1 receptor expression in fasted rats was also depressed by administration of exogenous CCK.

Conclusions: (1) Cannabinoid CB1 receptors are expressed by rat vagal afferent neurones. (2) CB1 expression is increased in fasting, and is downregulated by CCK. (3) CCK modulation of CB1 receptor expression may contribute to control of appetite.

110 ACUTE PHYSICAL AND PSYCHOLOGICAL STRESS AND ITS INFLUENCE ON AUTONOMIC OUTFLOW TO THE GUT IN IRRITABLE BOWEL SYNDROME

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Background: Stress is likely to influence symptoms in the irritable bowel syndrome (IBS). We studied the effect of acute physical and psychological stressors on symptoms, visceral sensitivity, and gut specific autonomic tone in healthy volunteers and patients with IBS.

Methods: 24 patients (20 women) with constipation predominant IBS (Rome II criteria) and 12 healthy volunteers (8 women) underwent either a physical (cold water hand immersion) or a psychological (dichotomous listening to music) stressor on two separate visits. Assessments included: perception of stress (visual analogue scale); psychological state (Hospital Anxiety and Depression); systemic autonomic tone (heart rate and blood pressure); gut specific autonomic tone (laser Doppler flowmetry of rectal mucosal blood flow (RMBF)); and visceral sensitivity (anal and rectal electrosensitivity).

Results: The IBS group reported higher levels of perceived stress at baseline ($p<0.01$). *RMBF* fell during physical stress by 29.6 (SD 2.8) % and 28.7 (3.9) % ($p=NS$), and during psychological stress by 24.4 (2.1) % and 23.5 (4.3) % ($p=NS$) in IBS and control groups respectively. *Rectal perception* thresholds decreased during physical stress (23.2 (6) % *v* 0.6 (3) % (IBS *v* control group, $p<0.05$)), as did *rectal pain* thresholds (27.0 (4)% *v* 1.3 (5)% (IBS *v* control group, $p<0.001$)) During psychological stress, *rectal perception* thresholds decreased (19.4 (6) % *v* 8 (6) % (IBS *v* control group, $p<0.01$)), as did *rectal pain* thresholds (28.4 (4) % *v* 3.4 (3.8) % (IBS *v* control group, $p<0.001$)). There was no correlation between changes in sensitivity and autonomic tone.

Conclusions: Acute physical and psychological stress alters gut specific autonomic tone in both normal volunteers and IBS patients, and is associated with an increase in visceral sensitivity in IBS only. Heightened sensitivity with similar autonomic tone suggests a mechanism for visceral sensation independent of autonomic nerves. The stress response was similar in both healthy and IBS groups, arguing against the notion of an imbalance of autonomic nerves in IBS.

111 GASTRIC ELECTRICAL STIMULATION (GES) FOR SEVERE GASTROPARESIS—INTERIM RESULTS FROM A UK REGISTRY

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Introduction: Gastroparesis is a chronic condition characterised by delayed gastric empting in the absence of mechanical obstruction. Some patients do not respond to medical treatment, suffer chronic nausea and vomiting, and may require invasive supplemental nutritional support. Additionally, in diabetic patients gastroparesis can make maintenance of normal blood glucose levels a challenge. Gastric electrical stimulation (GES) represents a new surgical option for the treatment of severe gastroparesis. The system consists of an implantable pulse generator and two intramuscular electrodes, which are inserted into the muscular layer of the stomach. We are presenting interim results from a prospective registry.

Methods: To date nine patients (5 female, 4 male; mean age 32 years, SD 14.3) with documented gastroparesis as determined by gastric emptying studies have been implanted. Aetiology of gastroparesis was idiopathic in 4 and diabetic in 5 patients. The primary complaint was vomiting. Patients were symptomatic for an average of 6 years (SD 3.3). All patients were resistant to medication. Four patients required nutritional support via J-tube and 1 by TPN. Implantation was performed by laparotomy in 5 patients and laparoscopy in 4.

Results: The median vomiting frequency improved from 25.0 episodes/week (range 7.0–48.0) at baseline to 1.5 (range 0–7.0) ($p<0.05$) at the last follow up (mean 7.0 months). The number of hours patients experienced nausea declined, although the changes did not reach statistical significance. In two patients the benefit was only temporary. Two patients had their J-tube removed shortly after implantation. One patient died six months after implantation of a spinal abscess secondary to longstanding MRSA colonisation. No other major adverse events have been reported.

Conclusions: Our preliminary data support that GES has a potent antiemetic effect. Further studies and more long term data will be required to determine the full potential of this new treatment option.

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112 PATTERNS OF β-CATENIN STAINING AND DOWNSTREAM TARGETS OF β-CATENIN/TCF/LEF TRANSCRIPTION REVEAL MODES OF GROWTH OF COLORECTAL ADENOMAS: EVIDENCE AGAINST ''TOP DOWN'' AS A MAJOR COMPONENT OF CLONAL EXPANSION

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Background: The top down concept of the clonal expansion of colorectal adenomas (Shih, *PNAS* 2001;**98**:2640–5) has been quick to seize the imagination of workers in the field. However, we have shown early bottom up spread, and found top down in only a few larger adenomas (Preston. *Can Res* 2003;**63**:3819–25). Here, we analyse a large cohort of different adenoma types to establish its prevalence.

Methods: 116 tubular, 47 tubulo-villous, and 58 villous adenomas from 87 patients were available, measuring from 5 mm to 3.6 cm in diameter. Sections were stained, using immunohistochemistry, for β-catenin to assess nuclear translocation, for CD44 and carbonic anhydrase II and β-catenin dependent and independent gene products. Cell proliferation was assessed by staining for Ki67 with MIB-1, and for mcm2.

Results: (1) 42% of all adenomas showed nuclear β-catenin; (2) only 18 adenomas (8%), mainly tubulo-villous, showed top down spread, where adenomatous epithelium was seen growing down pre-existing crypts, but growth from the surface between crypts was frequently seen; (3) growth by budding or fission was common in all types; (4) 11%, of mainly villous adenomas, showed basal crypt nuclei with nuclear β-catenin, while more superficial cells showed cytoplasmic and membranous staining; and (5) a reversal of proliferative architecture in adenomatous crypts was frequently seen.

Conclusions: (1) top down spread is rare and associated with a villous format; (2) adenomatous crypts are mainly formed by fission or by growth between pre-existing crypts to form new crypts; (3) the loss of nuclear β-catenin indicates positional regulation; and (4) reversal of proliferation is a feature of larger lesions. We conclude that crypt fission and budding, and the formation of new crypts from the surface, are the main modes of expansion of colorectal adenomas.

113 DERANGED SMOOTH MUSCLE α-ACTIN: A BIO-MARKER OF INTESTINAL PSEUDO-OBSTRUCTION. A CONTROLLED MULTINATIONAL CASE SERIES AND ONTOLOGICAL STUDY

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Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a severe motility disorder associated with significant morbidity. Several histopathological (neuropathic and myopathic) phenotypes have been described, but only a single adult with jejunal smooth (circular) muscle α-actin deficiency. We present a prospective multinational case series of 131 fully clinically and physiologically (including prolonged (24 h) ambulatory jejunal manometry) characterised CIIP patients from 3 European centres investigating smooth muscle α-actin deficiency as a biomarker of this disease. Immunohistochemical localisation of actins and other cytoskeletal proteins were performed on laparoscopic full thickness jejunal biopsies and compared with adult controls. Distribution of α-actin was also characterised in other gut regions and in the developing human alimentary tract. 36/131 (27%) CIIP patient biopsies had absent (n = 27) or partial (n = 9) jejunal smooth muscle α-actin immunostaining in the circular muscle layer. In contrast, smooth muscle α-actin-staining was preserved in the longitudinal muscle and in adult controls. Comparative study of other adult alimentary tract regions both in disease/health, and fetal small intestine suggest that expression of smooth muscle α-actin can be switched on and off both spatially and temporally. These findings taken together indicate the ability to modulate α-smooth muscle actin expression, evident in development, is maintained in adult life and may be influenced by disease rendering it a valuable bio-marker even in the absence of other structural abnormality.

114 HUMAN HEPATIC SINUSOIDAL ENDOTHELIAL CELLS (HSEC) INTERACT WITH HEPATITIS C VIRUS E2 GLYCOPROTEIN VIA DCSIGN AND LSIGN

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Introduction: LSIGN, a type 2 C type lectin expressed on HSEC can bind with high affinity to HCV E2 glycoprotein. A closely related homologue DCSIGN, expressed only on dendritic cells and a subset of macrophages, has similar binding affinity to HCV E2 glycoprotein.

Aim: To study the role of DCSIGN and LSIGN expression in sinusoidal endothelial cell interaction(s) with HCV E2.

Methods: Primary HSEC were isolated from donor liver tissue using standard methods. DCSIGN and LSIGN expression was detected by RT-PCR, flow cytometry, and immunohistochemistry. Intact liver sections were used to identify the localisation of cells expressing DCSIGN and LSIGN and those capable of interacting with HCV E2 by immunofluoresence and confocal microscopy.

Results: DCSIGN was expressed on HSEC and in portal tracts, distinct from LSIGN, which was only located on HSEC. Isolated primary HSEC also expressed DCSIGN. HCV E2 staining of liver sections co-localised with LSIGN and DCSIGN expression. Furthermore, E2 binding to sinusoids and portal tracts was inhibited by anti DCSIGN and anti LSIGN antibodies. Stimulation of primary isolated HSEC with IL-4 upregulated DCSIGN and LSIGN expression, leading to an increase in E2 binding.

Conclusion: 1) We report for the first time the expression of DCSIGN on HSEC. 2) The different distribution of DCSIGN and LSIGN in the liver and the ability of both lectins to bind HCV E2 suggest a complementary role in HCV trapping and uptake within the liver. 3) The ability of IL-4 to increase DCSIGN expression suggests a novel mechanism by which this cytokine may regulate HCV cell attachment and infectivity. 4) The expression of DCSIGN in portal areas suggests an additional role in leukocyte recruitment in the portal inflammation of chronic HCV infection. The cell specific regulation of expression and function of HCV receptors provides potential novel pharmacological targets for antiviral therapy.

115 RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL OF ORAL ALOE VERA GEL FOR MILD–MODERATELY ACTIVE ULCERATIVE COLITIS

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Background: The herbal preparation aloe vera has been claimed to have anti-inflammatory effects and, despite a lack of evidence of its therapeutic efficacy, is widely used by patients with inflammatory bowel disease. We have undertaken a double blind, randomised, placebo controlled trial of the efficacy and safety of aloe vera gel for the treatment of mild to moderately active ulcerative colitis.

Methods: 44 patients were randomly given oral aloe vera gel or placebo, 100 ml twice daily for 4 weeks, on a 2:1 ratio. Primary outcome measures were clinical remission (Simple Clinical Colitis Activity Index (SCCAI) score $\leqslant 2$), sigmoidoscopic remission (Baron score $\leqslant 1$), and histological remission (Saverymuttu score $\leqslant 1$). Secondary measures were changes in SCCAI (improvement = fall of $\geqslant 3$ points; response defined as remission; or improvement), and in Baron score, histology score, haemoglobin, platelet count, ESR, CRP, and albumin.

Results: Clinical remission, improvement, and response occurred in 9 (30%), 11 (37%), and 14 (47%) of 30 patients given aloe vera, compared with 1 (6%) ($p = 0.09$, odds ratio 5.6 (0.6–49)), 1 (6%) ($p = 0.06$, OR 7.5 (0.9–66)), and 2 (13%) ($p < 0.05$, OR 5.3 (1.0–27)), respectively, of 14 patients taking placebo. SCCAI and histological scores fell significantly during treatment with aloe vera ($p = 0.01$, $p = 0.03$, respectively) but not with placebo. Sigmoidoscopic scores and laboratory variables showed no significant differences between aloe vera and placebo. Adverse events were minor and similar in both groups of patients.

Conclusion: Oral aloe vera taken for 4 weeks produces a clinical response more often than placebo; it also improves histological disease activity and appears to be safe. These encouraging results suggest that further evaluation of the therapeutic potential of aloe vera gel in inflammatory bowel disease is warranted.

Gastrointestinal physiology free papers 116–119

116 DOES A 48 HOUR BRAVO PH STUDY FACILITATE THE DIAGNOSIS OF GASTRO-OESOPHAGEAL REFLUX DISEASE

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Background: The Bravo capsule has the potential to diagnose GORD in patients who refuse or are intolerant of conventional pH monitoring. It provides 48 hours of data and allows patients to continue normal daily activities and eating, reducing the impact of modified activities associated with a naso-oesophageal catheter.

Aim: To determine if 48 hour Bravo pH studies facilitate the diagnosis of GORD.

Method: 40 patients underwent Bravo pH monitoring. Percentage total, erect and supine time pH <4, and DeMeester scores were compared between day 1 and day 2. Diagnosis of GORD was made when pH <4 for $\geqslant 4\%$ total time, $\geqslant 6\%$ erect time, $\geqslant 2\%$ supine time or DeMeester score $\geqslant 14.2$.

Results: 32 patients had GORD. There was no significant difference between day 1 and day 2 median total time pH <4 (7.0 and 6.6%, $p = 0.33$), erect time pH <4 (8.0 and 7.5%, $p = 0.23$), supine time pH <4 (1.0 and 1.5%, $p = 0.27$), and DeMeester scores (22.75 and 24.25, $p = 0.76$). Two patients (5%) with normal results on day 1 were diagnosed with GORD on day 2. Twelve patients refused conventional pH monitoring: 11 had GORD. Three patients had normal conventional tests: all had GORD.

Conclusion: 48 hour Bravo pH studies provide only a marginal advantage over 24 hour studies but can diagnose GORD in a substantial number of patients not diagnosed by conventional testing.

117 GASTRO-OESOPHAGEAL REFLUX DISEASE, LUMEN DIAMETER, AND AGE

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Background and Aims: Gastro-oesophageal reflux disease is characterised by abnormal reflux and a multifactorial pathophysiology. It has been suggested that the disease is to some extent a function of age. There is also limited knowledge of the role played by

oesophageal lumen diameter. The aim of this study was to investigate the relationship between age and maximum lumen diameter (MLD) of the distal oesophagus in patients with gastro-oesophageal reflux disease.

Methods: For 31 patients (mean age 47, range 22–69) referred with a clinical diagnosis of gastro-oesophageal reflux disease the lumen diameters were measured from a series of controlled swallows during computerised fluoromanometry. For each swallow the MLD was measured using manometry transducers as reference points. These results were compared with the age of the patient.

Results: The MLD, which ranged from 1.5 cm to 2.77 (mean = 1.94 cm, sd = 0.32 cm), increased significantly with age ($p = 0.0007$). The results were even more significant when comparing age with the widest diameter at the most distal transducer ($p = 0.0002$). In the 9 patients with oesophagitis the correlation between MLD and age was stronger ($r = 0.667$).

Conclusion: This study demonstrated a change in oesophageal diameter with advancing age. These changes were most apparent distally, approximately 7 cm from the lower oesophageal sphincter. These results support the concept of presbyoesophagus, that is, ageing of the oesophagus. The study also highlights that oesophageal morphology may play a role in the pathogenesis of gastro-oesophageal reflux disease.

118 THE EFFECT OF PHOTODYNAMIC THERAPY (PDT) ON OESOPHAGEAL MOTILITY IN BARRETT'S OESOPHAGUS

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Aim: Barrett's oesophagus is the major risk factor for oesophageal adenocarcinoma and ablative techniques may reduce the chances of its development. PDT using aminolaevulinic acid (ALA) has been shown to effectively achieve mucosal ablation with good long term response, but it is unknown whether this treatment has an effect on oesophageal motility. It has been suggested that PDT may worsen oesophageal motility, and the aim of this study was to assess differences before and after PDT in oesophageal body motility parameters in the treated and untreated oesophageal areas.

Abstract 118

Measure	Pre PDT (mean (SD))	Post PDT (mean (SD))
Prox. resting pressure (cmH_20)	−2 (4)	1 (4)
Distal resting pressure (cmH_20)	−1 (5)	−2 (4)
Proximal amplitude (cmH_2O)	52 (18)	54 (26)
Distal amplitude (cmH_2O)	68 (24)	65 (26)
% Proximal peristalsis	66 (37)	78 (27)
% Distal peristalsis	72 (32)	83 (18)
% Study time pH<4	2.9 (4.8)	1.1 (1.3)

Methods: Standard water perfused manometry was carried out on Barrett's patients currently in a mucosal ablation trial using PDT. PDT was performed using 5-aminolaevulinic acid (ALA) at a dose of 30 mg/kg, followed by laser endoscopy under sedation 4–6 hours later using a windowed balloon applicator and red (635 nm) light at 68 mW/cm^2, with a total fluence of 85 J/cm^2. The median length of Barrett's was 4 cm (range 2–6). Parameters measured were proximal and distal oesophageal resting pressures, wave amplitude, and percentage proximal and distal peristalsis on water bolus swallowing. Proton pump inhibitor (PPI) therapy was given to all patients throughout the study, and 24 hour pH studies carried out before and after PDT.

Results: Twelve patients have been studied before and after complete ablation of the Barrett's segment (10 males; median age 56, range 31–81 years). No significant differences were found in oesophageal body motility in the untreated (proximal) or treated (distal) oesophageal areas after PDT (Wilcoxon signed rank test) (see table).

Conclusion: PDT mucosal ablation does not appear to impair oesophageal function either in the treated (distal) or the untreated (proximal) area of the oesophagus. The sustained response seen after PDT ablation does not appear to be due to improved oesophageal clearance.

119 UNPRECEDENTED PREVALENCE OF LARYNGOPHARYNGEAL REFLUX (LPR) AMONG GASTRO-OESOPHAGEAL REFLUX (GORD) SUFFERERS. IS UNDERDIAGNOSIS LEADING TO MISMANAGEMENT OF GORD PATIENTS?

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Introduction: Laryngopharyngeal reflux (LPR) is present if there are three or more episodes of laryngeal pH<5 in a 24 hour period. The larynx is exquisitely sensitive to peptic injury and LPR has been implicated in the aetiology of many conditions including laryngeal carcinoma. LPR has been considered an otolaryngological (ENT) condition as fewer than 10% of ENT-LPR patients manifest oesophagitis or Barretts oesophagus. We undertook to assess the prevalence of LPR in a cross section of ENT and gastro-oesophageal reflux (GORD) patients.

Methods: 46 consecutive patients with signs or symptoms of acid related reflux disease referred for pH studies underwent dual channel pH testing to evaluate oesophageal and pharyngeal acidity. Results were correlated with endoscopic findings. Wilcoxon was used for statistical analysis.

Results: There were 13 ENT and 33 GORD referrals. 43% of all patients were found to have laboratory evidence of LPR. Pharyngeal pH<5 (upright position) $p = 0.003$. Pharyngeal pH<5 (supine) $p = 0.001$. Total pharyngeal pH<5, $p = 0.0006$. Thirty three patients had a positive DeMeester score, 19 of whom had LPR. Of these 26% had Barretts oesophagus. Only 3 of 13 ENT referrals demonstrated LPR whereas 57% of documented GORD patients had LPR.

Conclusion: LPR is far more prevalent among GORD sufferers than is currently realised, and there may also be a significant association with Barretts oesophagus. As standard therapy for GORD is insufficient to adequately treat LPR, the majority of GORD patients continue to suffer LPR. Dual channel pH testing may be indicated in all GORD patients to identify this substantial sub-population and optimise their management.

Inflammatory bowel disease 120–123

120 SYNBIOTIC CONSUMPTION INCREASES EXPRESSION OF MRNA FOR HYDROGEN SULPHIDE DETOXIFICATION ENZYMES

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Introduction: Bacterial metabolism of oxidised sulphur containing compounds has been linked to ulcerative colitis (UC). Probiotics have been shown to be useful in the treatment of UC, but the therapeutic mechanisms are unclear.

Aims: To study the effects of a synbiotic on the expression of mRNA for the hydrogen sulphide (H_2S) detoxification enzymes rhodanese, mercaptopyruvate sulphurtransferase (MST), and sulphite oxidase (SO).

Methods: In a double blind pilot study, eight UC patients were given a synbiotic preparation (combination of inulin (12 grams per day) and 2×10^{11} *Bifidobacterium longum*) and four UC patients were given a placebo for four weeks. Rectal biopsies were taken prior to starting the trial, and at the end of the experimental period. PCR primers for mRNA of the H_2S detoxification enzymes were used to identify and quantitate specific mRNA in rectal tissue using real time PCR (iCycler). The housekeeping gene GAPDH was used to standardise results.

Results: The mean age for the synbiotic group was 46.1 years old (range 24–67) and the mean age for the placebo group was 37.3 years old (range 26–59). Enzyme mRNA levels in both groups before treatment were comparable. The Wilcoxon signed rank test showed rhodanese and MST mRNA levels were significantly increased after synbiotic treatment ($p = 0.028$ and $p = 0.017$, respectively), but no statistical difference was observed for SO pre- and post-synbiotic treatment ($p = 0.237$). In the placebo group, there was no significant difference between the enzyme mRNA levels pre- and post-treatment.

Conclusion: The synbiotic increased synthesis for mRNA of H_2S detoxification enzymes, which could be a possible mechanism of its therapeutic benefit. This is a pilot study with small number of patients,

and a large double blind randomised trial will now be done to confirm these results.

121 CINNAMON AND BENZOATE FREE DIET AS PRIMARY TREATMENT OF ORO-FACIAL GRANULOMATOSIS

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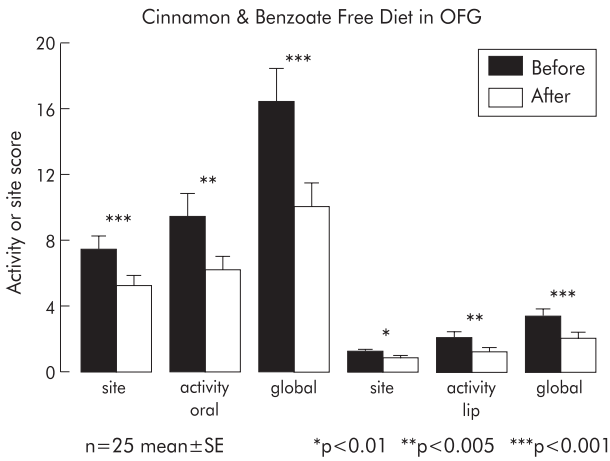
Background: Oral-facial granulomatosis (OFG) is a chronic inflammatory disorder characterised by inflammation in a variable number of sites in the oral cavity. Its cause remains unclear, but a possible role of sensitivity to dietary components, specifically benzoates (preservative in fizzy drinks) and cinnamon (common flavouring agent), has been proposed. The relationship between OFG and Crohn's disease remains unclear but a number of cases of OFG have co-existent gut inflammation. The aim of this study was to investigate the benefit of dietary exclusion of cinnamon and benzoates in patients presenting with OFG.

Methods: 25 patients (11 female, median age 36 years) attending a joint oral medicine/gastro clinic with a diagnosis of OFG were offered a cinnamon and benzoate free diet as their primary treatment. Patients were given verbal and written advice by a dietitian to follow the diet for a minimum of 6 weeks. Response was assessed using an oral activity scoring system (sites affected and severity at each site) pre and post dietary therapy.

Results: Significant improvements in oral inflammation were seen on the diet at 3 months. Improvement in lip activity was less marked than oral activity. Gut inflammation did not predict a response to the diet.



Abstract 121

Conclusions: A cinnamon and benzoate free diet appears to offer genuine benefit in OFG and can be reasonably considered as initial therapy in mild or moderate cases.

122 THIOPURINE METHYL TRANSFERASE ACTIVITY PREDICTS BOTH TOXICITY AND CLINICAL RESPONSE TO AZATHIOPRINE IN INFLAMMATORY BOWEL DISEASE: THE LONDON IBD FORUM PROSPECTIVE STUDY

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Background: Thiopurine methyl transferase (TPMT) deficiency increases the catabolism of azathioprine (AZA) to cytotoxic thioguanine nucleotides, leading to increased toxicity. Theoretically, higher TPMT activity should also predict a poor response to treatment but this has only been suggested in retrospective studies. In this study, we report the first multicentre prospective study of the role of TPMT in adult patients with IBD.

Methods: 189 patients (115 CD, 74 UC, median age 37 years) were recruited to a trial of AZA initiated at 2 mg/kg. Clinicians were blinded to TPMT activity although patients with zero activity were excluded. Adverse events and clinical response (Harvey-Bradshaw index, Truelove & Witts score, successful steroid withdrawal) were recorded over a 6 month study period. TPMT activity was measured by tandem mass spectroscopy.

Results: 75 patients (39%) developed adverse reactions requiring withdrawal or reduction in dose. Heterozygous TPMT deficiency was strongly associated with adverse effects (81% *v* 36% χ^2 p=0.005) particularly myelotoxicity and nausea. Among those completing the 6 month study, TPMT activity was inversely related to clinical response. (TPMT 25–40 units=55/90 (61%) TPMT >40 units 6/21 (29%) χ^2 p=0.015).

Conclusions: This prospective confirms the importance of TPMT deficiency in predicting toxicity on AZA, particularly nausea and myelotoxicity. However, the study also demonstrates the additional role of TPMT in predicting clinical response to AZA and predicts that those with highest TPMT activity should receive higher than standard doses or alternative treatment.

123 IS THERE A RELATIONSHIP BETWEEN *NOD2* POLYMORPHISM AND RESPONSE TO POLYMERIC ENTERAL FEED IN CHILDREN WITH CROHN'S DISEASE?

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Background: Crohn's disease (CD) may arise in part from an aberrant immune response to intestinal flora. NOD2 is an intracellular lipopolysaccharide receptor involved in cellular response to bacterial products. Polymorphisms of the *NOD2* gene have been associated with CD. Exclusive enteral nutrition (EN) is successfully used to treat children with CD. The mechanism of action may involve a change in bowel flora. We hypothesised that there may be an association between response to EN and *NOD2* status.

Aim: To determine whether clinical response to EN in children with CD is associated with the 3020insC *NOD2* polymorphism.

Methods: Children with newly diagnosed CD were treated with EN (Modulin, Nestle). Response or non-response to EN was determined by conventional clinical criteria. Following treatment *NOD2* status was determined using TAQMAN (ABI Systems).

Results: 36 children with newly diagnosed CD were recruited. 5 had localised disease not requiring EN, and 1 was treated with steroids. 30 were treated exclusively with EN. DNA was available from 26 patients; median age 12.8 (6.7–15.0) years; 18M 8F; 17 Caucasian, 4 Asian, 2 Afro-Caribbean, 2 Jewish, and 1 Asian/Caucasian. Of these, 4 DNA samples failed the TAQMAN assay. No patients were homozygous for the variant allele, 4 (18% were heterozygotes).

Conclusion: Response to EN, and frequency of the NOD2 3020insC polymorphism were similar to other reports. NOD2 3020insC allele status was not found to be associated with response to EN. Other NOD2 susceptibility polymorphisms (SNP8, SNP12) are being examined.

Abstract 123 The response to EN and *NOD2* allele status for the 22 patients

	NOD2 3020insC +ve	*NOD2 3020insC−ve*
Responded to EN	3	16
Did not respond to EN	1	3

p 0.45 (Fisher's exact test)

Service development free papers 124–133

124 ENDOSCOPY WAITING TIMES, THE 2 WEEK WAIT AND STAGE OF UPPER GI CANCER

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Introduction: There are approximately 17 000 new cases of gastric and oesophageal cancer in the UK each year. Survival is poor due to late stage at diagnosis. From 2000, patients meeting criteria for suspected cancer have to be seen by a specialist within 2 weeks. In our institution, significant service improvements have allowed a reduction in waiting times for routine gastroscopy from 27 weeks to <1 month. We have evaluated the effect of the 2 week wait and improvement in endoscopy services on stage of diagnosis of upper GI cancer.

Methods: Data were collected regarding routine gastroscopy waiting times from 1997 to 2003 and the proportion of upper GI cancer patients with early (stage 1 or 2) disease between 1998 and 2002. Presenting symptoms were reviewed for all 55 cases of early cancer presenting to one surgeon (MPL) between 2000 and 2003 to establish the proportion of these fulfilling the 2 week wait criteria.

Results: A sizeable reduction in routine endoscopy waiting times (1997–99: 24–27 weeks; 2001–2003: 2–6 weeks) was achieved along with an increase in the proportion of cancers diagnosed early from 19% to 23% ($p<0.001$). Of the 55 cases of early cancer, 35% met the 2 week wait criteria although only 2 (4%) were referred through the system.

Discussion: Since the introduction of the 2 week wait for upper GI cancer, the proportion of patients with early disease has improved. However, the majority of patients with early disease do not meet these criteria and of those that do most are diagnosed via different routes. Attempts to reduce routine endoscopy waiting times are likely to have the greatest impact on survival of patients with upper GI cancer.

Abstract 124

2 week wait criteria	Anaemia	Dyspepsia	Haemorrhage	Other
19 (35%)	13 (24%)	10 (18%)	6 (11%)	7 (13%)

125 IS OPEN ACCESS ENDOSCOPY APPROPRIATE IN THE CONTEXT OF THE 2 WEEK WAIT?

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Background: Open access gastroscopy has been available in our trust to GPs since 1996. This is restricted to patients >45 years of age. Current guidelines suggest that gastroscopy is unnecessary in the majority of patients under 55 years of age. A fast track service (2 week cancer wait) has been running for 3 years and has a 10% pick up rate for malignancy.

Methods: Data were collected retrospectively from the Endoscopy Records System.

Results: See table. In 3 years only three cancers (0.2% of procedures) were detected via open access gastroscopy. 10 benign gastric ulcers (0.7% of procedures) and 36 duodenal ulcers (2.7% of procedures) were detected, and 22 cases of severe oesophagitis or benign strictures (1.7% of procedures).

Abstract 125

Year	Total number of gastroscopies	Open access gastroscopies	Open access <55 years of age
2000	3301	569	300 (52.7%)
2001	3277	459	233 (50.8%)
2002	3356	320	164 (51.3%)
total	**9934**	**1384**	**697 (52%)**

Summary and Conclusions: The majority of open access gastroscopy referrals detect no significant pathology. Half were undertaken in patients <55 years of age and would not meet current referral criteria. A ''test and treat'' policy would have been appropriate in these patients. All cases of cancer detected would have met fast track criteria (and would have been endoscoped within 2 weeks rather than the 8–12 weeks waiting time for open access endoscopy during the study period). We conclude that open access endoscopy is no longer appropriate in the context of the 2 week fast track service for suspected upper GI cancer.

126 IMPACT OF ENDOSCOPY SERVICES REDESIGN IN NEWCASTLE UPON TYNE HOSPITALS NHS TRUST

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Introduction: The process of redesign and standardisation of Newcastle Endoscopy Services, which performs 14 500 endoscopies per year, led us to submit a successful bid to become a pilot site for the National Endoscopy Programme in September 2002.

Method: Following process mapping the data collection phase commenced, which provided baseline information. Two compulsory measures involved monitoring percentage booked cases and DNA rates. Government targets are DNAs less than 2% and booked cases 100% by January 2004. Local milestones were set to achieve these targets.

Results: Baseline data revealed percentage of booked cases at Freeman Hospital (FRH) 28%, Newcastle General Hospital (NGH) 13%, and Royal Victoria Infirmary (RVI) 38%. DNA rates at FRH 8%, NGH 11%, and RVI 5.3%. All patients attending outpatient clinics at the RVI received booked appointments at pre assessment and this was introduced at the FRH in October 2002. Systems were established to introduce partial booking across all three sites for surveillance patients in December 2002 and all other patients by April 2003. By May 2003 the percentage of booked cases had increased to FRH 95%, NGH 95%, and RVI 94%. DNAs in June 2003 had decreased to FRH 3%, NGH 4.5%, and RVI 1.6%. The decrease in DNA rate followed the trend of increased booking and met the local milestones. The introduction of booking led to a sharp increase in clerical staff workload due to patients ringing the unit for their appointments. This has proved unsustainable with current staffing levels, leading to some partial booking systems being halted until further resources for clerical staff can be identified. Data from September 2003 shows that percentage of booked cases has decreased to FRH 20%, NGH 39%, and RVI 42%. DNA rates have increased to FRH 5.4%, NGH 6.7%, and RVI 4.4%.

Conclusion: Partial booking effectively reduces DNA rates but to be sustainable requires adequate funding.

127 THE IMPACT OF A DEDICATED ENDOSCOPY REFERRAL FORM, INCORPORATING THE ROCKALL SCORE, ON THE MANAGEMENT OF PATIENTS WITH ACUTE UPPER GASTROINTESTINAL HAEMORRHAGE (UGIH)

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Background: Acute UGIH has an incidence of 103/100 000 in the UK. The Rockall score is a validated means of stratifying severity, and the risk of rebleeding and mortality. The clinical use of this score should facilitate patient management.

Aim: To evaluate the impact on patient management of a new dedicated endoscopy referral form, based on the Rockall score.

Method: A new referral form for patients with UGIH was introduced in April 2003. Form development included piloting among users before delivery to the medical admissions unit. No specific dissemination or implementation strategies were utilised. The case notes of 40 randomly selected patients admitted with UGIH in the 4 months prior to April 2003 were compared with 40 patients admitted following the introduction of the new form. Results were analysed using χ^2 and *t* tests.

Results: There were no significant differences between the two groups in terms of age, sex, endoscopic diagnoses, or Rockall scores. There was a trend towards earlier endoscopy in patients managed using the new form. 80% *v* 62.5% were endoscoped within 36 hours ($p<0.10$). The average hospital stay for patients with a simple GI bleed was reduced (2.1 *v* 4.0 days, $p=0.04$). The average stay for all patients was reduced (5.3 *v* 8.8 days, $p=0.05$). No low risk patients (Rockall score <3) were readmitted with a GI tract related problem. No deaths occurred in low risk patients. Total mortality was 10%, with no significant difference between the groups. No death was the result of a GI cause.

Conclusion: Incorporating a validated means of patient assessment into clinical practice had a favourable effect on patient management. The new form appears to highlight patients requiring early endoscopy, and empowers clinicians to make evidence based decisions about discharge without any detrimental effects. Earlier investigation and appropriate early discharge are both highly desirable outcomes. Such opportunities to positively modify clinical management must be actively sought.

128 POTENTIAL IMPACT OF BSG COLONOSCOPY SURVEILLANCE GUIDELINES ON THE PROVISION OF COLONOSCOPY SERVICE

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Introduction: Demand for colonoscopy is increasing and currently exceeds supply. Surveillance for high risk premalignant conditions is recommended to reduce the incidence of colorectal cancer and is a major indication for colonoscopy. Recent guidelines from the BSG and NHS Modernisation Agency for endoscopy have suggested how to optimise this overburdened service.

Aims and Methods: Retrospective audit performed to identify patients in colonoscopy surveillance programmes and to determine if the interim follow up was in accordance with BSG guidelines. The potential impact of instituting these guidelines on our colonoscopy service was assessed. Completion and complication rates were determined.

Results: 425 surveillance colonoscopies were identified. Indications for surveillance were polyp follow up (n=146), inflammatory bowel disease (n=194), family history of colorectal cancer (n=77), and CRC follow up (n=8). In relation to BSG guidelines, planned follow up surveillance colonoscopy was inappropriate in 53.8% of patients. Of these, 59% were planned too early by a mean time of 41.4 months. 17% of patients were deemed not to require any colonoscopic follow up. By instituting these guidelines the total number of patients requiring surveillance colonoscopy next year has fallen from 75 to 38 with a potential cost saving of £28K next year. In addition, waiting times for diagnostic colonoscopy has fallen to within the 13 week recommendation. Completion and complication rates in this group were 87% and 0%, respectively.

Conslusions: By implementing BSG guidelines to a previously ad hoc system of colonoscopy surveillance, we have reduced the total number of surveillance colonoscopies in our department next year by 49%. This has resulted in improved patient access times for diagnostic colonoscopy, and increased time resource for endoscopic training. Simple but effective measures such as this will be required to minimise the impact of colorectal cancer screening when it is introduced in the UK.

129 HAVE BSG GUIDELINES ON POLYP FOLLOW UP REDUCED ENDOSCOPY WORKLOAD? RETRO- AND PROSPECTIVE AUDIT

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Background and Aims: In our unit, patients are referred for polyp follow up colonoscopy by a variety of clinicians, many of whom are not gastroenterologists. We felt that too much follow up was requested, so we audited referrals against the 2003 BSG Guidelines.

Methods: Colonoscopies performed for polyp follow up over a one year period prior to the release of BSG Guidelines were analysed retrospectively. Cases were identified from an endoscopic database and colonoscopy reports were used to calculate follow up interval, as recommended by the BSG Guidelines. Colonoscopy requests were also prospectively analysed over a six month period after publication of the guidelines. Compliance to guidelines was assessed by comparing the actual time to referral for polyp follow up compared with the recommended interval.

Results: Average actual follow up intervals were 21 months pre-guidelines and 26 months post-guidelines. According to the guidelines, the mean follow up interval should have been 37 and 40 months, respectively. There were 8 unnecessary procedures prior to guidelines, and 4 after.

Conclusion: According to the guidelines, a large proportion of patients were referred for polyp follow up too early. In our hospital, the guidelines have so far made only a modest change among gastroenterologists (which may not be sustained), and little or no impact among other referring groups, generating a significant excess endoscopy workload.

130 IMPROVED PATIENT ACCESS TO LOWER GI SERVICES IN A DISTRICT GENERAL HOSPITAL: THE RESULTS OF SERVICE RE-DESIGN

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Aim: To improve patient access to lower GI services in a busy district general hospital rectal clinic by service re-design

Methods: A multidisciplinary team was established that analysed capacity and demand, implemented booked admissions, involved NHS Direct, mapped the patient pathway from GP to outpatient clinic, developed the skills of a nurse endoscopist, and investigated patient feedback by walk-throughs and focus groups.

Outcomes: Analysis of capacity and demand resulted in pooling of clinic lists with a subsequent reduction of overall waiting times. 100% of 2 week rule patients were seen within the required time frame and waiting time for routine appointments fell by 8 weeks. All patients attending rectal clinics were partially or fully booked resulting in DNA rates falling from 10–4%. The use of NHS Direct to pre-screen patients and give out information before attending for flexible sigmoidoscopy decreased patient enquiries to the clinic and decreased inappropriate attendances, however a pre-visit telephone reminder had no effect on DNA rates. Mapping the patient pathway and re-organisation of outpatient clinic templates led to increased activity in clinic with reduction of delays, long waits, and clinic over-runs. A nurse endoscopist was trained to perform independent colonoscopies resulting in a reduction of list cancellation and a more holistic approach to patient care. Patient feedback by walk-throughs, questionnaires, and focus groups led to simplified patient information leaflets and a better understanding of the process.

Conclusions: A multidisciplinary approach to service re-design can improve the efficiency and effectiveness of outpatient services.

131 IS THE DEVELOPMENT OF A NURSE COLONOSCOPY SERVICE WORTHWHILE

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Introduction: The need for high quality examination of the colon is increasing in the UK, fuelled by the ''2 week rule'' for cancer diagnosis, rectal bleeding clinics, and open access colonoscopy service for GPs. We have responded to these pressures by training LH as a colonoscopist, practicing independently since August 2000.

Aims and Methods: To assess the impact and diagnostic yield of a nurse colonoscopy service between August 2000 and 2003. The findings, caecal intubation rate, and complication rate, were reviewed retrospectively from the computer record.

Results: Number of colonoscopies performed annually by LH were 481 of 1834 (26%), 671 of 1916 (35%), and 771 of 2032 (38%). The crude caecal intubation rate was 85%, 82%, and 82%; but when ''corrected'' for obstructing lesions and poor preparation the rates were 92%, 91%, and 90%. The findings at colonoscopy are shown in the table. There were no serious complications with diagnostic and therapeutic procedures.

Conclusions: 1) Nurse colonoscopy is safe. 2) A well trained nurse colonoscopist can achieve caecal intubation rates of 90%, with 40% of procedures showing some abnormality. 3) The throughput and waiting times for colonoscopy have both improved. We recommend this service as the demand for colonoscopy increases, particularly with population screening for colon cancer on the horizon.

Abstract 129

Percentage of patients followed up in compliance with guidelines

Referring group	Pre-guidelines (n=102)	Post-guidelines (n=59)	Number of patients
Gastroenterologists	31%	57% (p<0.05)	77
Surgeons	45%	36% (p=NS)	74
Other referrers	50%	50%	10
Overall	35%	49% (p=0.1)	161

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Colonoscopy findings:	2001	2002	2003
Normal	297	364	490
Polyps	121	169	165
Divericular disease	95	152	146
Cancer	16	14	18
I.B.D.	31	25	31
Angiodysplasia	4	1	1

132 C-BASE—AN ELECTRONIC MANAGEMENT TOOL FOR HEPATITIS C

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Effective management of HCV infection relies on the collaborative effort of a multidisciplinary team. Integration of this activity within a complex timetable of unrelated commitments is costly in terms of diary synchronisation and the pulling of medical records. We set out to create an electronic HCV patient record using readily available information technology components to encapsulate all stakeholder requirements.

Methods and Specification: 1) Affordable for multicentre implementation by restricting components to Microsoft Windows & Office XP, SQL and Exchange servers. 2) Satisfy Caldicot data security specifications for multi-centre use. 3) Link to legacy PAS servers. 4) Define a treatment status property for the HCV patient class to map the patients journey through the healthcare system. 5) Store all parameters necessary for patient management, including histopathological images and graphical data displays. 6) Automate diary task creation to synchronise with PDAs. 7) Support aggregate data views by treatment status and genotype.

Results: The objectives were achieved within the framework of a Microsoft Access Project by supplementing the object library with Outlook, Excel, Graph, and OLE automation libraries. Security is provided by Windows NT logon and SQL server database roles. ADO connection with PAS servers is supported and repeating diary entries on the Exchange server can be created with the Outlook Task object. Linked histopathological images may be viewed with Microsoft Photoeditor and Microsoft Excel with the Query Analyser installation and OLAP link displays pivot charts and tables for audit and cost projection. Identical real time views can be created with Microsoft Front Page to be studied anywhere on the network in a web-browser. One clinician and two nurses manage a cohort of 350 patients with a fortnightly paperless meeting.

Conclusion: An affordable Microsoft Integrated Solution comprising Office XP, SQL, and Exchange servers could manage the nation's HCV burden.

133 THE IMPACT ON ERCP SERVICE FROM THE INTRODUCTION OF RADIAL ENDOSCOPIC ULTRASOUND

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Aims: ERCP has been regarded as the gold standard for evaluation of the biliary tract but is associated with significant complications, particularly pancreatitis. Recently it has been suggested that normal findings at endoscopic ultrasound (EUS) in those with suspected CBD stones may obviate the need for ERCP. We report the impact on ERCP service from introduction of EUS in our centre.

Methods: All EUS carried out over a 52 month period were examined. For this study we were interested in impact on service for those patients suspected to have bile duct stones and excluded those carried out for non-biliary pathology, for example pancreas tumour staging or diagnosis and assessment of chronic pancreatitis.

Patients: 367 EUS carried out, 186 for suspected bile duct stones. There were 53 males:132 females, mean age 53 years (range 17–87). All were referred for ERCP by secondary care physicians or surgeons due to ''biliary pain'' (52%), abnormal LFTs (62%), abnormal USS (73%), or a combination of these; 25% were post cholecystectomy.

Results: Following EUS forty two patients were recommended for ERCP with definite or suspected abnormality: 64% had a sphincterotomy for confirmed stones, 19% had sphincterotomy on recommendation of EUS evidence, 12% had other EUS suspected abnormalities confirmed. There was one ERCP failure and one non-therapeutic ERCP. Nine other patients had ERCP without EUS recommendation: five normal, one suspected biliary dyskinesia and three with stones/debris at ERCP (all three >160 days post EUS).

Conclusions: The majority of the study group would have had ERCPs for investigation if EUS had not been available. The introduction of EUS avoided 134 out of 185 potential ERCPs: clinical follow up was available for 18 months minimum. Of the nine patients who had ERCP during follow up the three found to have ductal stones/debris were referred five months after the EUS. EUS has a positive impact in terms of selection for therapeutic ERCP and is likely to have a beneficial effect on complications and cost of an ERCP service.

Plenary posters 134–153

134 SEP53 AND AG-2 MAY ACT AS PROTO-ONCOGENES IN BARRETT'S METAPLASIA

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The adverse environment the oesophagus is exposed to induces heat shock proteins. A novel stress response was found operating in the oesophageal epithelium. This involves down regulation of the classical heat shock protein HSP70 and up regulation of the novel stress proteins SEP70 (squamous epithelial heat shock protein 70) and SEP53 (squamous epithelial heat shock protein 53) in response to a variety of stressors including low pH. In addition we have identified anterior gradient-2 (AG-2) as a protein upregulated in Barrett's tissue. AG-2 is associated with intestinal goblet cells, localises to the plasma membrane protein, and is over expressed in primary breast cancers. HSPs can interact with cell cycle control elements such as p53 to allow cell survival. We investigated this role for these proteins.

Study: Gene constructs for SEP53 and AG-2 were transfected into H1299 cells in a colony proliferation assay. In this assay oncogenes would increase cellular proliferation and therefore colony formation. Both SEP53 and AG2 behaved in a proto-oncogenic manner like mutant p53 in the colony proliferation assay. We then went on to examine a large panel of patients for the expression of SEP53 and AG-2 in lysates from biopsies. We examined normal oesophageal epithelium (n = 10), squamous epithelium from Barrett's patients (n = 20), and from Barrett's metaplasia (n = 19). SEP53 was uniformly expressed in squamous epithelium, but very variably expressed in Barrett's metaplasia. AG-2 was uniformly expressed in Barrett's metaplasia but also in some samples of squamous epithelium from both non-refluxers and Barrett's patients. This suggests a possible role for SEP53 and AG-2 in enhancing proliferation rates in Barrett's metaplasia and squamous oesophageal mucosa, with AG2 playing a greater role in Barretts while SEP53 functions predominantly in squamous tissue. Whether the expression of both proteins in the same cell would be synergistic for proliferation and dysplastic change requires further investigation.

135 DOES THE LENGTH OF THE COLUMNAR LINED OESOPHAGUS (CLO) CHANGE WITH TIME

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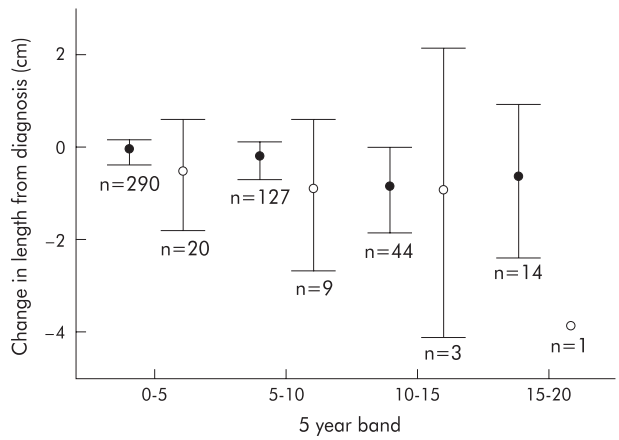
Introduction: Conflicting results have emanated from small series' as to whether CLO segment length varies over time. This study addresses this issue from a large UK series with prolonged follow up.

Patients and Methods: Lengths of CLO segment and histology at diagnosis and at subsequent endoscopies were abstracted from medical records of 310 patients registered with UKBOR. To minimise inter-observer variability, segment length measurements were averaged over five year bands, and variations from the diagnostic lengths were examined in patients who developed high grade dysplasia or



Abstract 135

adenocarcinoma (HGD/AC) (○), and those who did not (●). The average number of recorded CLO lengths was 4.12 (SD 2.51), and average follow up period 5.45 (4.31) years, total 1358 endoscopies.

Results: Overall, there was no significant change in mean CLO segment length over time periods up to 20 years in either group. The graph shows the mean change of length and 95% confidence intervals.

Conclusions: This study demonstrates that overall, mean CLO segment length does not change significantly over time periods up to 20 years both for uncomplicated CLO and in those who developed HGD/AC.

136 PERCUTANEOUS ENDOSCOPIC GASTROSTOMY INSERTION: CAN CURRENT ANTIOBIOTIC PROPHYLAXIS GUIDELINES BE EFFECTIVE

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Introduction: Percutaneous endoscopic gastrostomy (PEG) feeding tubes are frequently placed to allow nutrition of dysphagic patients (particularly following stroke). Peristomal infection occurs in 15–30% of patients and may be as high as 65% in patients with malignancy. The BSG currently recommends antibiotic prophylaxis with either a cephalosporin or co-amoxiclav to prevent infection. Recent studies suggest that the majority of infections occur with MRSA, an organism resistant to both types of antibiotics. In Norwich, we do not routinely cover PEG insertion with antibiotics. We have studied the rate of peristomal infection and the organisms involved.

Methods: 46 consecutive patients undergoing PEG insertion between May and September 2003 were studied. Patients were followed up for 30 days and data collected regarding morbidity and mortality. Endpoints for this study were rates of peristomal infection and positive peristomal swabs.

Results: 78% of PEGs were inserted for stroke, 20% for a variety of other neurological causes of dysphagia and 2% for malignancy. 30 day mortality was 20%. 33% of patients developed a peristomal infection (67% received systemic antibiotics and 33% topical antibiotics). Positive swabs were taken from 35% of patients (MRSA 81%, streptococci 25%, coliforms 13%, and anaerobes 6%).

Discussion: 28% of patients in this study grew MRSA from peristomal swabs. Similar rates of peristomal infection and MRSA infection have been found previously in the UK. Current antibiotic prophylaxis guidelines are unlikely to make any significant impact on peristomal infection rates while the commonest organisms involved are resistant. Use of broad spectrum antibiotics in this situation is likely to increase resistance and predispose to *Clostridium difficile* diarrhoea. Alternative strategies are required to reduce peristomal infections with MRSA.

137 UPPER OESOPHAGEAL SPHINCTER MANOMETRY AND 24 H PH MEASUREMENTS IN PATIENTS WITH GLOBUS SENSATION

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Introduction: Patients with globus sensation are usually referred to an ENT specialist for possible malignancy. However, in most patients, flexible laryngoscopy shows no abnormalities, and further management is often unclear. Most patients are treated for gastro-esophageal reflux (GOR) with acid suppression medication and further follow up is often unsatisfactory. Manometric examination of the upper oesophageal sphincter (UOS) may help in the differential diagnosis of crico-pharyngeal spasm and 24 h pH may be useful where globus is related to GOR. We performed oesophageal manometry including the UOS, to detect cryco-pharyngeal hypertension, using a multi-lumen catheter (Mediplus, UK) specially designed to measure radial pressures and sphincter dynamics, during normal station pull through procedure.

Methods: Fifteen patients underwent station pull thorough manometry. UOS and oesophageal body motility were measured simultaneously. During the measurement, patients underwent 10 5 ml water swallows and also a half marshmallow. UOS hypertension was determined as after swallow contraction amplitude >100 mmHg (Wilson *et al*, 1989). Twenty four hour ambulatory pH measurements were performed after the manometry to assess reflux.

Results: Seven patients had hypertensive UOS (median 111 mmHg, range 103–171 mmHg). Of those 7 patients, 3 also had pathological reflux (total percentage time pH<4 was 6.9%, 19.6%, 6.7%). Two had pathological reflux without UOS hypertension (11.8%, 13.7%). One patient was diagnosed as achalasia.

Conclusion: UOS manometry and 24 hour pH measurements have detected pathology in high proportion of patients (11 out of 15) with globus sensation. These investigations are therefore useful for managing patients with globus who had normal laryngoscopy. We now perform these examination as routine clinical procedures.

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138 CHARACTERISATION OF THE NOVEL OESOPHAGEAL SPECIFIC HEAT SHOCK PROTEIN SEP53

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The oesophagus expresses a distinctive set of heat shock proteins. This study aims to determine the function and regulation of one of these proteins—squamous epithelial heat shock protein 53 (SEP53)—and its relation to the disease process. SEP53 has an EF-hand calcium binding motif like that of the S100 family of calcium binding proteins. It is thought that this may be involved in protein activation. Monoclonal antibodies raised against SEP53 were analysed using purified SEP53 protein digested with trypsin. These antibodies constituted 3 classes showing distinctive bands with the digested protein. When binding strengths were analysed by ELISA all three classes bound with similar strength, increasing as the dilution decreased. Trypsin digestion of SEP53 protein $+/-Ca^{2+}$ and analysis by western blot using a SEP53 polyclonal antibody show a different band pattern, suggesting conformational changes in the presence of these ions. Cells were treated with 1 mM deoxycholic acid and tested for viability by trypan blue staining. Following a 6 hour treatment 18.6 (SD 13.9) % of an isogenic control remained viable while in SEP53 overproducing cells this was 61.2 (15.0) %, indicating that it may protect the cells. Biopsies taken from patients with no oesophageal pathology and from Barrett's patients were analysed by western blot using the SEP53 antibody. All samples from the pathologically normal patients expressed SEP53, and this was also true of squamous tissue biopsies from Barrett's patients. However, only one sample of the Barrett's metaplasia biopsies expressed the protein.

In conclusion SEP53 may be a calcium binding protein of the S100 family. It is present in normal squamous oesophageal tissue but absent in most but not all Barrett's cases and its presence increases the viability of the stable cell line in the presence of deoxycholic acid.

139 BILE FLOW AND COMPOSITION ARE MODULATED BY INTRAVENOUS GLYCINE IN AN IN VIVO WARM ISCHAEMIA REPERFUSION INJURY MODEL

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Background: Liver ischemia reperfusion (I/R) injury is a major complication of liver resection and transplantation. The cytokine release by activated Kuppfer cells (KCs) plays a central role and glycine inhibits KC activity. The effect of glycine administration on bile flow and composition following I/R has not been investigated.

Methods: A rabbit model of hepatic lobar warm I/R was used. Under general anesthesia, the sham group (n = 6) underwent laparotomy alone for 7 hours. The control I/R group (n = 6) underwent 60 min of left and median lobe inflow occlusion and 6 hours of reperfusion. The glycine I/R group (n = 6) underwent a similar procedure to controls after receiving glycine 5 mg/kg IV. Bile output was measured and composition analysed by proton magnetic resonance spectroscopy.

Results: Bile flow was reduced following I/R alone but was maintained in the glycine I/R group (108.3 (SD 28) *v* 2145.0 (11.4) μL/min/gm in the glycine group, p = 0.011) 6 hrs post reperfusion. Glycine administration prior to I/R was associated lower phosphatidylcholine (1.2 (0.8) *v* 3.0 (0.5) μmol/L in controls, p = 0.001) and lactate levels (8.1 (4.3) *v* 26.3 (7.8) μmol/L in controls, p<0.001) and increased bile acid (17.9 (2.8) *v* 8.9 (2.1) μmol/L in controls, p = 0.001), pyruvate (1.3 (0.3) *v* 0.7 (0.1) μmol/L in controls, p = 0.005), glucose (3.9 (0.9) *v* 1.6 (0.6) μmol/L in controls, p = 0.007), and acetoacetate levels (0.7 (0.1) *v* 0.4 (0.1) μmol/L in controls, p = 0.009) (p<0.001, glycine I/R *v* controls) on reperfusion.

Conclusion: 5 mg/kg IV glycine 1 hr prior to 60 min ischemia normalised bile flow and was associated with a significantly altered bile composition.

140 IS PROPHYLACTIC BANDING ALWAYS SAFE? RANDOMISED CONTROLLED TRIAL FOR THE PREVENTION OF FIRST VARICEAL BLEEDING IN CIRRHOTIC PATIENTS WITH CONTRAINDICATIONS OR INTOLERANCE TO B BLOCKERS

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Background and Aim: Endoscopic banding ligation (EBL) versus no therapy reduces the risk of first portal hypertensive bleeding, no significant complications being reported. We evaluated EBL in the prevention of first bleeding in cirrhotics intolerant/contraindications to b blockers.

Patients and Methods: Sample size of 214 was planned with all size varices. However, the trial was stopped after 52 randomised patients as there was more bleeding than expected in the EBL group. EBL group: 25 (M/F = 17/10, mean age 61 years, range 40–76, EBL group), 27 not treated (M/F = 21/4, mean age 63 yrs, range 43–76, NT group). Banding done by experienced endoscopists, 2 weekly until obliteration and then 3 monthly surveillance.

Abstract 140

	NT	BANDING
Small varices	Bleeding: 0/17 Death: 7/17	Bleeding: 1/14 Death: 3/14
Large varices	Bleeding: 2/10 Death: 4/10	Bleeding: 4/11 Death: 4/11

Results: No differences in baseline parameters of severity liver disease or endoscopic features. Mean follow up period of 17.7 months (range: 1–46): 5 bled EBL group (20%, 3 from variceal bleeding 11 and 17 days after banding and one during procedure, and two from gastropathy) and two NT group (7.4%, two from variceal bleeding). Deaths: Seven EBL/11 NT–non significant.

Conclusion: 60% of the bleeding in the banding group was probably iatrogenic, requiring stoppage of the study. EBL was no better than no treatment. This is the first study suggesting that EBL may be harmful as primary prophylaxis similar to sclerotherapy in the past.

141 FINE MAPPING OF THE 5q31 RISK HAPLOTYPE IN CROHN'S DISEASE

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We have previously demonstrated an association between the 250 kb risk haplotype on 5q31, CARD15 and early onset of CD.[1] However, the true susceptibility gene on 5q31 has yet to be identified due to the high degree of linkage disequilibrium (LD) across this region observed in a Canadian cohort.[2] Linkage disequilibrium, the non-random association between alleles at different loci, provides a powerful method for fine structure localisation of rare disease genes. We have used the approach of LD mapping on the 5q31 risk haplotype in our north European cohort in an effort to further narrow the genetic interval containing the disease causing mutation.

Five SNPs (2011, 2063, 2230, X100, and 3236) within the risk haplotype were genotyped in 254 unrelated Crohn's patients and 349 controls. These SNPs were selected on the basis of their position within discrete haplotype blocks as described by Daly *et al*.[3] Genotyping was performed by TaqMan allelic discrimination. Tests for Hardy-Weinberg equilibrium and case control association analyses were performed using χ^2 statistics and odds ratios, respectively. Haplotype frequencies were estimated with EHPLUS and LD between the three SNPs was calculated using coefficient Δ as a measure of association.

The results of the case control analysis show that only SNP 2063 is significantly associated with CD ($p = 0.003$). Analysis of LD coefficients confirms the haplotype structure as suggested by Daly *et al*[3] but also shows incomplete LD across the 250 kb risk haplotype observed by Rioux *et al*.[2] This difference has permitted the likely location of the disease causing gene to be narrowed down within the original 250 kb risk haplotype.

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142 COMPARISON OF HYDROGEN SULPHIDE DETOXIFICATION ENZYME MRNA EXPRESSION IN NORMAL AND ULCERATIVE COLITIS RECTAL MUCOSAE

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Introduction: Hydrogen sulphide (H_2S) produced in the colon is toxic to the colonic mucosa and may be involved in the pathogenesis of ulcerative colitis (UC). The exact pathway of H_2S detoxification in the colon is unclear but is thought to include the enzymes rhodanese, mercaptopyruvate sulphurtransferase (MST), and sulphite oxidase (SO).

Abstract 142

	UC	Non-IBD
Number of patients	10	10
Mean age (range)	24–69 (50.4)	39–72 (54.6)
Rhodanese median (interquartile range) (IQ range)	1.6 (0.20–5.70)	4.23 (2.56–15.18)
MST median (IQ range)	0.33 (0.12–0.61)	0.73 (0.44–6.88)
SO median (IQ range)	0.0204 (0.0004–0.0760)	0.0352 (0.0112–0.0551)

Aim: To assess whether there are differences in expression of rhodanese, MST, and SO mRNA in healthy rectal mucosa from patients without inflammatory bowel disease (IBD) and patients with UC.

Methods: Rectal biopsies were obtained from 10 non-IBD patients and 10 UC patients. PCR primers for mRNA of the detoxification enzymes were designed and developed. mRNA for each of these enzymes was identified and quantitated using real time PCR (iCycler). The house-keeping gene GAPDH was used to standardise the results.

Results: The Mann-Whitney test showed there were statistical differences for rhodanese and MST between non-IBD and UC patients ($p = 0.05$ and $p < 0.05$). There was no significant difference for SO between the two groups ($p = 0.624$).

Conclusion: The ability of UC mucosa to detoxify H_2S may be impaired. The low level of SO detected and the lack of difference between the two patient groups suggests that this enzyme does not play an important role in H_2S detoxification in the colon.

143 THE RIGHT AND LEFT CONUNDRUM: COLONOSCOPY OR FLEXIBLE SIGMOIDOSCOPY FOR THE INVESTIGATION OF ISOLATED RECTAL BLEEDING (IRB)?

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Background: Data to guide the clinician as to the choice between colonoscopy or flexible sigmoidoscopy are lacking in patients with isolated rectal bleeding (IRB). This may pose the greatest difficulty in younger patients with IRB, where the risk of neoplastic disease is slight but not absent.

Aim: To determine the burden of disease in the right colon in patients presenting with IRB.

Abstract 143

Pathology (path)	No. (%) (Total = 853)	Exclusive R sided path Total = 60	L sided path (Distal to splenic flexure) (Total = 543)	Of 187 pts with IRB & R sided path. <50 yr	Of 416 pts with IRB & R sided path. >50 yr
Mucosal Inflam.	138 (18%)	30 (50%)	108 (19.9%)	**17** (9%)	**13** (3%)
Polyps	82 (9.6%)	18 (30%)	64 (11.8%)	**7** (4%)	**11** (2%)
Tumour	31 (3.3%)	4 (7%)	27 (5%)	**1** (0.5%)	**3** (0.7%)
D D	214 (25.1%)	8 (13%)	206 (38%)	0	**8** (2%)
Haemorrhoids	138 (18%)		138 (25.4%)		
Normal	250 (29.3%)				

Pts, Patients; DD, diverticular disease.

Methods: We performed a one year retrospective analysis of 853 patients with IRB of who had a colonoscopy. Types of pathology identified included mucosal inflammation, polyps, tumour, diverticular disease, and haemorrhoids.

Results: Caecal intubation rate was 96% while terminal ileum was 52.4%. The median age of patients with exclusive right sided pathology was 58 years (range 36–90) compared with 63 years (range 18–93) for those who had only left sided pathology. 34 colonoscopies, needed to be performed to find one patient (less than 50 years) with significant right sided disease. In patients over 50 years of age, this figure was 24.

Conclusions: For patients presenting with IRB, left sided disease is 9 times more likely than right sided disease. However, for patients under 50 years the diagnostic yield is higher, particularly right sided inflammation (threefold) and polyps (twofold) detected only by colonoscopy. While right sided colonic carcinoma is an important diagnosis it is rare in all ages in this presenting group.

144 AN AUDIT OF THE WAITING LIST FOR SCREENING AND SURVEILLANCE COLONOSCOPY IN A DISTRICT GENERAL HOSPITAL

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Introduction: There is an 18 month waiting list for screening or surveillance colonoscopy. A recent pilot study in Kent reported that >25% of patients do not satisfy British Society of Gastroenterology (BSG) criteria[1] for screening or surveillance colonoscopy (SSC) and could be removed from the waiting list. An audit was therefore undertaken to determine whether patients could be safely removed from (AWH) waiting list using the BSG criteria.

Methods: Medical notes of 100 consecutive patients from the waiting list were searched (BHH) to determine the indications for SSC and compared with BSG criteria.

Results: Mean age of 100 patients was 52 (range 24–80); 55 were male. 9 of 9 patients with one first-degree relative with colorectal cancer (CRC) fulfilled BSG criteria for SSC, yet only 2 of these 9 were followed at the correct interval. 23 of 27 patients with two or more first-degree relatives with CRC fulfilled criteria, with 3 of 27 being followed at the correct interval. Patients with any other family history (n = 5) were not considered to fulfil criteria for SSC. Of 42 patients receiving SSC for adenomatous polyps, all fulfilled criteria and 39 were followed at the correct interval. All patients being followed up for inflammatory bowel disease (n = 13) fulfilled criteria and 10 were followed at the interval determined by BSG criteria. One patient with acromegaly fulfilled criteria for entry and follow up. One patient with a family history of HNPCC was entered onto the waiting list at an age considered not to fulfill BSG criteria.

Conclusions: This audit has shown that 10 of 100 patients on the AWH waiting list for screening or surveillance colonoscopy do not fulfil the BSG criteria. These patients could be removed from the SSC waiting list. In addition, in 36 of 90 (40%) patients on the waiting list, the follow up interval could be extended, thereby further decreasing the number of tests performed. These changes in practice do not involve any increase in resource allocation.

1. *Gut* 2002;**51**(Suppl V):v28.

145 A PROSPECTIVE AUDIT OF A 24 HOUR NURSE LED TELEPHONE HELPLINE SERVICE FOR GASTROENTEROLOGY PATIENTS

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Background: Patients with chronic gastroenterological conditions often have concerns and queries that may require medical input. These patients may have to wait to be seen in the outpatient clinic. In view of this, a nurse led telephone helpline service was established to offer information and support to these patients at our hospital in 2000.

Aim: To audit the uptake and outcome of the 24 hour nurse led helpline service, prospectively.

Methods: All telephone calls received and outcomes were documented in a diary. All calls were answered within 24–48 hours and, if necessary, the nurse specialist sought the advice of a doctor. This service has been audited annually, prospectively, for 3 years from 2000–2003.

Results: Female:male ratio = 2.5:1, median age 43 years (range 17–93 years). 89% of calls were received from patients with inflammatory bowel disease, 11% were from patients with other gastrointestinal disorders. 76% of all calls were resolved with advice alone, only 16% of patients required a hospital appointment, and only 1% required hospital admission. Other telephone calls were resolved with investigations being ordered, a prescription, or, rarely (0.4%), referring the patient back to their GP.

Abstract 145

	No of calls	Advice only	OPA made	Admit	Other
2000/01	501	387	60	9	57
2001/02	673	533	118	7	95
2002/03	670	483	114	4	83

Other, prescription, investigation or referred back to GP

Conclusion: A 24 hour telephone helpline service can improve access for patients to advice and support. This can be effectively managed by a nurse specialist. The majority of calls are resolved with advice alone, presumably leading to a reduced clinic attendance.

146 ARTIFICIAL BOWEL MARKERS AS A NOVEL METHOD TO ASSESS THE SENSITIVITY OF COLONOSCOPIC MUCOSAL VISUALISATION: A POTENTIAL AUDIT TOOL?

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Introduction: Colonoscopy is currently the gold standard for assessing colonic mucosal abnormalities. An important component of this is complete examination of the colon to the caecum. Equally important, however, is the ability to detect abnormalities within the length of colon examined, and no method has so far been described for assessment of this.

Aim: To assess the accuracy of detection of artificial bowel markers used as surrogates for small polyps.

Patients and Methods: Patients were randomly assigned to receive between none and four of each of two types of artificial bowel marker. Markers used were 5 mm squares of latex free rubber or metallic clips (Olympus HX-6U). These were placed on insertion of the colonoscope. At the limit of the endoscopy a second endoscopist, blinded to the number, type, and site of markers placed, performed the extubation. Eight operators took part in the study. Data regarding the number, type, and position of the markers on insertion and withdrawal were recorded as were insertion and withdrawal times.

Results: 190 markers (92 clips, 98 rubbers) were placed in 46 patients. The caecal intubation rate was 91%. Mean intubation time was

25 mins (5–60 mins) and withdrawal 17 mins (10–55 mins). Overall 145 markers (76.3%) were detected on withdrawal (clips 77.2%, rubbers 75.5%). There was no correlation between insertion or withdrawal times and the number of markers detected. Detection rates varied between endoscopists (69–87%), but this failed to reach statistical significance (p = 0.59). When marker detection rates were compared with caecal intubation rates for the same operators from a previous audit study, no correlation was found (p = 0.96). Markers placed at the hepatic flexure were significantly more likely to be missed (p = 0.04).

Conclusion: The skills required for identification of mucosal abnormalities may differ from those required to achieve caecal intubation. This would appear worthy of further detailed study.

147 IDENTIFICATION OF A NEW STRAIN OF *H PYLORI* INDUCING RAPID DEVELOPMENT OF GASTRIC CANCER IN THE MONGOLIAN GERBIL

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Introduction: Studies in Japan show long term infection of Mongolian gerbils with *H pylori* results in gastric adenocarcinoma. However, these results have not been reproduced with Mongolian gerbils in other countries. The aims of this study were to identify a colonising *H pylori* strain that stimulates high epithelial signalling responses and induces gastric cancer in the gerbil model.

Methods: An IL-8 luciferase reporter assay was used to evaluate the ability of *H pylori* clinical isolates from Guangxi, a region of China with a high incidence of gastric cancer, to stimulate IL-8 transcription in L5F11 gastric epithelial cells. Male gerbils (MGS/Sea) were orally inoculated three times with the selected *H pylori* strain and sacrificed at 6 and 30 weeks post infection to examine gastric pathology. Serum was assayed by ELISA for IgG antibodies to *H pylori*.

Results: The *cagA*+, *vacA* s1c m1 *H pylori* strain 3GX, which stimulates very high levels of IL-8 transcription in gastric epithelial cells, was selected for in vivo inoculation into gerbils. At 6 weeks, infection of 3GX strain was confirmed by culture and biopsy urease test. At 30 weeks post infection, 3 of 4 gerbils had thickened and polypoid gastric mucosa on gross inspection. On microscopy they revealed pan gastritis, severe epithelial hyperplasia, and high grade dysplasia with foci of intramucosal carcinoma. At 6 and 30 weeks gerbils were serologically positive for *H pylori* IgG antibodies.

Conclusions: This study confirms previous Japanese reports that *H pylori* infection induces gastric carcinoma in gerbils. In contrast to previous Japanese studies, where gastric cancer resulted 14–18 months post infection, infection with the 3GX strain results in gastric carcinoma by 30 weeks. The rapid development of gastric cancer with this Chinese strain will facilitate studies on the role of *H pylori* in gastric carcinogenesis.

148 EARLY LINEAR ENDOSCOPIC ULTRASOUND AND FINE NEEDLE ASPIRATION EXPERIENCE IN A DISTRICT GENERAL HOSPITAL

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Background: Linear endoscopic ultrasound (EUS) with fine needle aspiration cytology (FNA) is a relatively new modality of gastrointestinal investigation of limited availability in the UK.

Aim: To review the hurdles and pitfalls of starting a linear EUS and FNA service in a district general hospital and outline indications, early results, and complications.

Patients and Methods: 168 EUS cases were carried out between October 2001 and October 2003. An initial capital investment of £120 000 was required to set up the service. Seventy seven cases (45.8%) were extra contractual referrals.

Results: Indications for EUS/FNA: mediastinal 25/22, oesophageal 66/3, gastric 23/2, pancreas 38/16, biliary 10/6, miscellaneous 6/0. Complications: total = 5 (3% overall, 10% of FNA cases): 2 duodenal perforations, 1 acute pancreatitis, 1 infected para-pancreatic haematoma, 1 bleeding during cyst drainage. All complications occurred during the first year of experience. EUS investigations resulted in a significant influence on the management of patients in 150 cases (89.3%) and reversed previous clinical decisions in 65 cases (38.7%).

Discussion: Although the service was rapidly established resulting in a major referral rate, the difficult operator learning curve resulted in a 10% complication rate related to FNA in the first year, while there were no complications in the second year. EUS and FNA are valuable diagnostic modalities but have a significant (10%) complication rate related to FNA.

149 PROGNOSTIC SIGNIFICANCE OF ALARM SYMPTOMS IN PATIENTS WITH GASTRIC CANCER

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Background: The recently modified BSG guidelines advise that endoscopic investigation of dyspepsia in patients aged <55 years is only justified in the presence of alarm symptoms.

Aims: To determine the incidence and spectrum of alarm symptoms in patients with newly diagnosed gastric cancer, and to examine the relationship between presenting symptoms and outcome in a hospital with high incidence of gastric cancer.

Abstract 149

Results	Alarm symptoms	Control
Age median (range)	72 (27–93)	70 (35–86)
No aged <55 years	25 (10%)	6 (15%)
Stage IV cancer	137 (55%)	15 (35%)*
R0 gastrectomy	71 (28%)	18 (45%)**
5 year survival (%)	13	31**

*P = 0.04, **P<0.01.

Methods: All 290 patients presenting with gastric carcinoma between 1995 and 2003 were studied prospectively. The 250 patients (86%) with alarm symptoms were compared with the 40 patients with dyspepsia and/or pain without alarm symptoms.

Survival was inversely proportional to number of alarm symptoms at presentation (log rank 11.7, DF 4, p = 0.03). Univariate analysis of each symptom revealed that only anaemia (92 patients, 37%) predicted shortened survival ($\chi^2 = 5.81$, DF 1, p = 0.01). Of the 6 patients without alarm symptoms, five were aged between 46 and 54 years, and all remain alive and well after a median 58 months.

Conclusion: Alarm symptoms are absent in a significant minority of patients at diagnosis, and patients without them stand a better chance of potentially curative surgery and long term survival. For uncomplicated dyspepsia, restricting endoscopy to patients aged >55 years will delay diagnosis of potentially curable gastric cancer in the 46–55 age group. The original age threshold of 45 is safer practice in areas with high incidence of gastric cancer.

150 5-AMINOSALICYLIC ACIDS AND COLON RECTAL CANCER: A LARGE BRITISH EPIDEMIOLOGICAL STUDY

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The medical records of general practitioners (GPs) in the UK (from the General Practice Research Database) were used to evaluate the risk of colorectal cancer (CRC) in patients with a history of IBD prescribed aminosalicylates (5-ASA). In a nested case control analysis, each incident CRC case with any exposure to 5-ASA within 6 months of the CRC diagnosis was matched by age, sex, and calendar time to 6 control patients who were also exposed in that period. Patients were then classified according to regularity of use. Regular users were those who had received 6 or more 5-ASA prescriptions in the 12 months before. The analysis was controlled for body mass index, IBD duration, history of colorectal polyps, use of NSAIDs, paracetamol, aspirin, immunosuppressants, oral and rectal glucocorticoids, and prior GI hospitalisation, recorded colonoscopy, or number of GP visits for IBD symptoms in month 6 to 24 months before.

Of the 18 969 study patients, 100 developed CRC during 5-ASA exposure and most had a history of ulcerative colitis (n = 76). In the case control analysis, significant risk factors for CRC included history of colon/rectum polyps (crude OR 10.24 (95% CI 3.42 to 30.69)) and number of GP visits for IBD symptoms (1 symptom, 1.24 (0.74 to 2.06); 2 or more symptoms 2.70 (1.45 to 5.04)). Current use of NSAIDs was associated with a reduced risk of CRC, but this did not reach statistical significance (OR 0.80 (0.38–1.66)). Regular users of 5-ASA were found to have a decreased risk of CRC compared to irregular users (crude OR 0.67 (0.44 to 1.03); adjusted OR 0.60 (0.38 to 0.96)).

Regular users of sulfasalazine with 6–12 prescriptions before had an adjusted OR of 0.95 (0.22 to 4.11); with 13–30 prior prescriptions this was 0.41 (0.14 to 1.20) and with >30 prior prescriptions this was 0.77 (0.37 to 1.60). For mesalazine users, these figures were 1.13 (0.49 to 2.59), 0.30 (0.11 to 0.83), and 0.31 (0.11 to 0.84), respectively. In conclusion, these results support earlier work suggesting a possible preventative effect of 5-ASA in the development of CRC in ulcerative colitis.

151 BOTULINUM TOXIN AS A DIAGNOSTIC TOOL IN SPHINCTER OF ODDI DYSFUNCTION

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Introduction: Sphincter of Oddi dysfunction (SOD) represents a difficult diagnostic challenge. Sphincter of Oddi manometry is the gold standard diagnostic method, but this is technically difficult, carries significant risk, and possibly under diagnoses SOD as sphincter hypertension may be an intermittent phenomenon. A minority of cases may also be equivocal, in that high pressure is confined to only a short 2–4 mm segment of the sphincter. It is not clear if these cases represent true SOD, or are simply artefactual. Injection of botulinum toxin (BTX) directly into the sphincter has been proposed as a means of diagnosing SOD. We suggest it may be a useful adjunct to sphincter of Oddi manometry in difficult or equivocal cases.

Abstract 151

	ES responder	No response to ES
BTX responder	9	0
No response to BTX	0	2

Sensitivity and specificity = 100%. $p<0.05$ by Fisher's exact test

Methods and Results: 96 patients with suspected SOD were assessed prospectively over a 3 year period with sphincter of Oddi manometry and those found to have equivocal manometry (short segment hypertension, n = 13), persisting symptoms and normal manometry (n = 5), failed manometry (n = 2), and those judged to be at a very high risk of post-procedure pancreatitis (n = 1) were injected with 100u BTX directly into the sphincter. Endoscopic sphincterotomy (ES) was performed if patients reported a symptomatic improvement at 3 months. Further follow up at 3 and 6 months post ES was performed to gauge response. 21 patients received BTX, 19 were available to follow up. 11 patients improved symptomatically, of which 9 underwent ES. All 9 are symptom free at follow up. Of the 8 patients who received no benefit from BTX, 2 still underwent an ES. Both of these remain symptomatic.

Conclusions: BTX is a very effective means of anticipating response to ES when manometry is equivocal or in difficult cases. We plan a randomised trial to support these conclusions.

152 CAN HYPNOSIS BE USED TO INDUCE NAUSEA AND IS THIS ASSOCIATED WITH DELAYED GASTRIC EMPTYING

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Most laboratory based research into the effect of nausea on gastric functioning has been conducted using nausea evoking stimuli, such as circular vection.[1] The aim of this study was to determine whether the sensation of nausea can be successfully induced by hypnosis and whether this is associated with a delay in gastric emptying.

Methods: Gastric emptying was measured, using the ^{13}C breath test in 13 healthy volunteers (aged 20–34 years; 8 female); once while the subject received hypnotic suggestions of a sensation of nausea (active) and once while listening to relaxing music (control). The test conditions (active and control) were applied for 20 minutes between 40 and 60 minutes after ingestion of a flapjack meal (231 kcal) containing 150 mg of stable isotope [^{13}C-1] sodium acetate. The order of studies was randomised, and the intensity of nausea recorded on a scale of 0 to 10 (10 = max) every 5 minutes throughout the studies.

Results: Using hypnosis, nausea was successfully induced in 12 of the 13 subjects, reaching a maximum intensity of 7.5 (4.5–10) (median (range)). In 10 of these 12 subjects, gastric emptying was prolonged, such that the time for half of the meal to empty from the stomach ($T_{1/2}$) was significantly greater ($T_{1/2}$ = 139.6 min (mean)) than under control conditions ($T_{1/2}$ = 126.0 min; mean difference from active (95%CI): −13.6 min (−26.5, −0.7) min; p = 0.041). The subject who did not feel nauseous during hypnosis exhibited slightly faster emptying during this ($T_{1/2}$ = 117.5 min) compared with control ($T_{1/2}$ = 130.3 min) conditions; reducing slightly the overall significance for the whole group (n = 13: $T_{1/2}$ active: 137.9 min v $T_{1/2}$ control: 126.3 min; −11.5 min (−24.1, 1.0) min; p = 0.069).

Conclusions: Hypnosis can be used to successfully induce the sensation of nausea and is associated with a delay in gastric emptying. Hypnosis might provide an alternative way to study the effects of nausea in a laboratory based setting.

1. *Am J Physiol* 2001;**280**:G853.

153 POLYMORPHISMS IN THE ILEAL BILE ACID BINDING PROTEIN GENE IN SUBJECTS WITH DIARRHOEA

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Bile acid malabsorption is a relatively common cause of diarrhoea and is frequently secondary to resection of the terminal ileum. Idiopathic (primary) bile acid malabsorption can present as post infective, or diarrhoea predominant irritable bowel syndrome. Specific transport systems to reabsorb bile salts are expressed in the ileum and a rare mutation associated with diarrhoea has been described in the apical sodium linked bile transporter expressed in the brush border membrane. We have investigated in subjects with chronic diarrhoea whether polymorphisms could be detected in another transporter in this system, the ileal bile acid binding protein gene (IBABP, gene symbol *FABP6*), expressed in the cytoplasm.

Genomic DNA was prepared from 23 patients with chronic diarrhoea, including 9 where SeHCAT testing had confirmed bile salt malabsorption, and 23 control subjects without diarrhoea. Approximately 1 kb of the promoter was amplified and sequenced in all patients. Additionally in the patients with diarrhoea, we sequenced the four exons and intron/exon junctions.

Several different single nucleotide polymorphic (SNP) sites were identified in the promoter region of the IBABP gene. 12 of the 46 subjects had a SNP in the promoter. No patient had more than one site. One SNP was found in 7 subjects: 5 with diarrhoea and 2 controls. Another was found in 2 with diarrhoea and 2 controls. Both of these SNPs may represent consensus transcription factor binding sites. A number of other SNPs were identified in the exonic regions in diarrhoea patients, including 2 SNPs which altered the translated sequence of IBABP.

We conclude that genetic variation is common in the IBABP gene and is a potential cause of functional abnormalities in bile acid absorption. Further investigations will determine the precise role of these polymorphisms in idiopathic bile acid malabsorption and chronic diarrhoea.

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154 WHAT ARE THE ENDOSCOPIC REQUIREMENTS OF A CANCER CENTRE?

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Introduction: The Endoscopic Unit at the Chelsea and Westminster Hospital, a teaching hospital, treated 6000 patients last year. We provide a service to the local population of south west London and also to the Fulham Road branch of the Royal Marsden Hospital, a tertiary referral cancer centre which had 5236 new patients, 5611 inpatients admissions, 9757 day cases, and 50 629 outpatient attendances in the past year. The endoscopy requirements of the general population are well described but the demands of a population with cancer are not known.

Aims and Methods: To describe the elective endoscopy requirements of a cancer centre. We maintained a prospective register of all patients referred from the Royal Marsden Hospital to our unit over a period of six months. Emergency procedures were not included.

Results: Between January 2003 and June 2003, 224 patients were referred from the Royal Marsden Hospital. 135 were men, median age 66 and 89 women, median age 57 (range 18–100). Diagnostic

procedures performed included colonoscopy (n = 91), upper GI endoscopy (n = 45), flexible sigmoidoscopy (n = 29), endoscopic ultrasound (n = 23), and endoscopic retrograde cholangio-pancreatography (n = 12). Therapeutic procedures included ERCP (biliary stents/sphincterotomy/stone extraction) (n = 22), placement of percutaneous endoscopic gastrostomy (n = 14), balloon dilatation of oesophageal strictures (n = 11), oesophageal, gastric, duodenal or colonic stent insertion or laser therapy (n = 8), and banding of oesophageal varices (n = 1). Most of the stenting procedures were palliative (n = 18). All patients were treated as outpatients. Four patients were admitted for observation after their investigation. All others were discharged home or back to the Royal Marsden Hospital.

Conclusions: Cancer therapy is increasingly effective with improved cure rates and survival. Cancer centres increasingly require diagnostic, palliative, and therapeutic endoscopic support as part of the acute and follow up management of patients. This study suggests that 9% of new patients at a cancer centre will require endoscopic intervention and the range of procedures and skills required is wide.

155 THE COST EFFECTIVENESS OF OPIOD ANALGESIA FOR COLONOSCOPY: A PILOT STUDY COMPARING PENTAZOCINE, PETHIDINE, AND NALBUPHINE HYDROCHLORIDE

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Background: Various types of intravenous analgesia are used for colonoscopy. Cost per vial varies by up to 300%, depending on the type of analgesia used.

Method: Over a 3 week period patients were randomly assigned to receive pethidine, pentazocine, or nalbuphine hydrochloride as analgesia for colonoscopy. This analgesic was administered alongside standard sedation (midazolam). 20 patients were assigned to each group. Perceived intra-procedure pain scores were recorded both by the nursing assistant and by the operator. Pain was recorded between 0 (no pain) and 5 (intolerable pain). All patients completed post procedure satisfaction questionnaires.

Results: In total 83% of patients were completed by all grades of operators. Mean pain scores were; nalbuphine hydrochloride = 2.35, pethidine = 1.3, and pentazocine = 1.94. No significant difference was seen for length of time spent in the recovery area. In the pethidine group no patients reported nausea or vomiting, 5% actually reported experiencing pain, and 40% documented bloating/wind. In the pentazocine group 5% reported nausea and vomiting, 25% bloating/wind, and 10% pain. In the nalbuphine hydrochloride group 31% reported pain, 37% nausea and vomiting, and 79% bloating/wind.

Conclusions: Despite nalbuphine hydrochloride being over 300% more expensive, and pentazocine more than 100% more than pethidine, they did not offer any benefit. Pethidine remains the best tolerated, most effective, and cheapest analgesic for colonoscopy.

156 DIAGNOSING ABDOMINAL TUBERCULOSIS: LAPAROSCOPY, THE INVESTIGATION OF CHOICE

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Background: The clinical presentation of abdominal tuberculosis (TB) is usually protean with non-specific abdominal and other general complaints. The aim of our study was to identify specific features in the history and clinical presentation as well as the investigations that help to establish a definitive diagnosis of abdominal TB.

Patients and Methods: Medical records of 36 patients with documented diagnosis of abdominal TB were reviewed retrospectively. Among others, details of history, clinical presentation, investigations, and diagnostic procedures performed were identified.

Results: 32 of the patients were of Asian origin, predominantly from the Indian sub-continent, an area endemic for TB. Abdominal pain and significant weight loss were the most common presenting complaints. Only two patients were found to have concurrent pulmonary TB. Clinical examination had revealed very non-specific abdominal signs. A low haemoglobin and a raised C-reactive protein (CRP) were the most consistent findings in more than 90% of the patients. The tuberculin test (Mantoux) was of very poor diagnostic value as was Zeil-Nielson staining of ascitic and other bodily fluids for acid-fast mycobacteria. An ultrasound scan of the abdomen revealed findings consistent with TB in only a third of the patients it was performed. CT scan of the abdomen fared only marginally better. A laparoscopy, although performed after some delay as a last resort in most patients, proved to be most diagnostic of abdominal TB in more than 90% of the patients it was performed. It also had the advantage of histological confirmation of visual findings consistent with abdominal TB.

Conclusion: Abdominal tuberculosis can be difficult to diagnose. We advocate that in patients with the relevant background and clinical history, laparoscopy is the investigation of choice.

157 APPROPRIATENESS OF COLONOSCOPY AND BARIUM ENEMA IN THE INVESTIGATION OF COLORECTAL DISEASES

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Aims: Appropriateness of barium enema and colonoscopy in the diagnosis of colorectal disease is essential for the rational utilisation of available resources in the NHS. The increase in demand coupled with the shortage of experienced colonoscopists is putting more pressure and is negatively affecting the waiting time for the procedure. We need therefore to focus more on appropriate colonoscopy requests.

Methods: The indications for barium enema and colonoscopy of 100 patients each were collected from the referral forms sent between January and February 2002 from the radiology and endoscopy departments. Indications and appropriateness were determined according to the American Society of Gastrointestinal Endoscopists (ASGE) guidelines.[1]

Results: Appropriateness of barium enema was 100%. While that for colonoscopy was 74% (that is, nearly 1:4 colonoscopy requests were inappropriate). The most common inappropriate requests for colonoscopy were altered bowel habit 65%, abdominal pain 23%, and weight loss 12%.

Conclusion: TGH performs 3.96 colonoscopies/1000 population/year. GPs in Trafford and Salford refer between 1000–1500 patients/year for rectal bleeding. In TGH 26% of colonoscopies were inappropriate. Altered bowel habit, constipation, abdominal pain, and weight loss are not appropriate for colonoscopy as the diagnostic yield is low. In TGH 12% of barium enemas are done for incomplete colonoscopies. The colonoscopy completion rate is 61.9% (M. Al-Gailani, Colonoscopy at Trafford 2002, personal data). Barium enema is safer and less expensive than colonoscopy; therefore the indications for its use are broader. Abdominal pain, diverticular disease, and non-specific symptoms of altered bowel habit, weight loss, and constipation are better candidates for barium enema. In mutually appropriate indications, the choice depends on factors such as age, fitness, and likely diagnosis. Preference of the patient and availability of the procedure are additional factors. Surveillance following bowel surgery is a new added indication for colonoscopy in our study not included in the ASGE guidelines. It is suggested that colonoscopy requests are to be verified by a consultant and that the request forms should include appropriateness indications for guidance. Colonoscopy completion rates are to be improved by paying attention to adequacy of bowel preparation and better training for colonoscopist.

1. Levine MS, Sor S, Yin D, *et al*. Barium enema and colonoscopy: appropriateness of utilization in a Medicaid population. *Abdominal Imaging* 1997;**22**:41–44.

158 AN ANALYSIS OF 2906 COLONOSCOPIES; CONDITIONS OF PRACTICE IN A DISTRICT GENERAL HOSPITAL

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Aims: To identify indications, results, complications, and completion rates for colonoscopy in a district general hospital.

Methods: Retrospective study based on a computer database of all colonoscopies done between October 1998 and February 2002 in Trafford General Hospital, Manchester.

Results: There were 2906 colonoscopies done. Average yearly colonoscopies were 855. Completion rates ranged between 55.5% and 78.3% with an average of 61.9%. This was found to be related to experience. There were 5.5% procedure failures: not prepared 66%, patient intolerance 33%, and 1% equipment failure. Indications for colonoscopy were: polyp surveillance 19%, rectal bleeding 10%, altered bowel habit 9%, abnormal investigation 8%, diarrhoea 8%, family history of colorectal cancer 5%, abdominal pain 5%, and assessment of inflammatory bowel disease 4%. In all 42% were normal and 58% abnormal, 28% were for surveillance while 72% were diagnostic. Commonest diagnosis was polyps 24%, diverticular disease 18%,

ulcerative colitis 7%, colorectal cancer 3%, and Crohn's disease 2%. Of the 107 colorectal cancers diagnosed, the indication for colonoscopy was rectal bleeding 25%, abnormal investigation 23%, change of bowel habit 15%, polyp re-assessment 10%, rectal mass 5%, and anaemia 5%. Intra-procedural complications were 31 (1%): bleeding 10, hypoxia 4, discomfort 15, and respiratory depression 2. Those were not found to be related to experience.

Conclusion: Completion rate is dependant on experience while intra-procedural complications are not. Polyps are the commonest finding while rectal bleeding is the commonest indication for colonoscopy in colorectal cancer diagnosis.

159 IS IT COST EFFECTIVE TO REDUCE NON ATTENDANCE RATE FOR ENDOSCOPIC SERVICES?

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Background: The NHS Modernisation Agency Endoscopy Project requires participating centres to achieve a 2% did not attend (DNA) rate by December 2003. The project defines a DNA as a patient who does not turn up for an appointment or who cancels within 24 hours. The DNA rate at the start of the project for this trust was around 5%.

Methods: For three months the hospital notes of outpatients booked for endoscopy in the main endoscopy unit (75% of work load) were examined. Information was collected on age, sex, ethnic group, referral route, and appointment booking method. Demographics were worked out for attenders and DNAs. In a subsequent six week period, patients who DNAed were contacted by telephone using a structured interview so that DNA reasons could be further examined.

Results: The DNA rate for the initial three months was 5.5% with no difference according to referral route. A significantly higher DNA rate was seen in the Asian population (12.3%) compared with the rest (4.3%). The highest DNA rate was among males of working age. It was surprising to note that a lower DNA rate of 2% was seen in patients who had no choice in their appointment date compared with 6% in those who had ''booked'' appointments (that is, those who had full consultation about appointment date). Of 42 patients who DNAed it was possible to contact 28. Of these DNAs, only 32% (n = 9) might have been avoided if additional administrative processes were in place (such as reminder letters or telephone calls 2 weeks prior to appointment date). The remaining 68% (n = 19) were assessed to be unavoidable DNAs due to reasons such as illness, death, and other circumstances beyond the patient's control.

Discussion: A higher DNA rate was observed in the Asian population but this was not thought to be due to language difficulties. The difference in DNA rate between ''booked'' and ''non-booked'' appointments can be explained by longer waiting times for the ''non-booked'' appointments. The target DNA rate of only 2% is unlikely to be achieved even if costly administrative changes are put in place.

160 ARE PATIENTS' PREFERENCES FOR SEDATION AT GASTROSCOPY INFLUENCED BY PRECEDING PATIENTS' DECISIONS?

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Background and Aim: When patients are offered a choice of being sedated or not for gastroscopy, it is not known whether such decisions are influenced by the decision and experience of preceding patients on the same endoscopy list. This question was addressed in an endoscopy unit where pre- and post-procedure patients are mixed and free to communicate.

Methods: 87 endoscopy sessions (predominantly outpatient diagnostic sessions) over a 10 month period were studied. Patients who required therapeutic procedures, were having lower GI endoscopy, or who were inpatients were excluded. The order for the remaining 503 patients on the endoscopy lists and their sedation decisions were noted and analysed.

Results: 236 (47%) patients were male, 267 (53%) female. Mean age was 56.4 years. After excluding patients having therapeutic or lower GI procedures and inpatients, each endoscopy list had 4 to 9 (mean 5.7) patients. 315 (62.6%) patients chose to be unsedated, 188 (37.3%) preferred sedation. Men were more likely to be unsedated, 170 (72%), than women, 158 (59%), $\chi^2 = 9.1$, $p < 0.01$. Age did not influence sedation decisions. Mean ages of sedated and unsedated patients were 58.5 years and 56.5 years, respectively. If the first patient on the list was sedated, 36% of subsequent patients on such lists were sedated. This proportion was not different to the 38% of subsequently sedated patients on lists where the first patient was unsedated ($\chi^2 = 0.14$, ns). Similarly there was no difference in the proportion of subsequent patients requesting sedation or no sedation in the lists where the first two patients were sedated and the lists where the first two patients where unsedated ($\chi^2 = 0.04$, ns). Even if all the first three patients were sedated or unsedated, this did not influence sedation choice of subsequent patients on the list.

Conclusion: A patient's decision to have sedation or not during a diagnostic gastroscopy is not influenced by the decision of preceding patients on the same endoscopy list. Men are more likely to be unsedated.

161 PATIENT AND ENDOSCOPIST VIEWPOINT OF BOWEL PREPARATION FOR LOWER GI ENDOSCOPY

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Background: The NHS Modernisation Agency Endoscopy Project is looking at endoscopy services. At this trust there is a large discrepancy in waiting times for lower GI endoscopic procedures between medical and surgical teams. Bowel preparation pre procedure differs between the teams. If a unified waiting list is going to be achieved the bowel preparation needs to be standardised.

Methods: Patients were invited to complete a survey prior to their procedure. Endoscopy records were reviewed for outcome and assessment of bowel preparation. Efficacy of bowel preparation was subdivided into adequate, poor, or poor/failed. Patient view and efficacy were related to the type of bowel preparation.

Results: Questionnaires were completed by 729 patients in whom efficacy assessment was also available. Significantly more patients found Klean-Prep (2–4 litres) (±senna) (n = 416) unacceptable (16.2%) or unbearable (16.7%) compared with only 2.7% unacceptable and 3.1% unbearable with picolax (400 ml)(n = 256). They were also less likely to drink all the preparation (klean-prep 9.5% *v* picolax 0.8%). Taste improvement was suggested by 25% of patients taking klean-prep compared with only 4% of those taking picolax. Side effects (including nausea, retching, vomiting, or headache) were reported in 54% taking klean-prep, 42% taking picolax, and 28% of the phosphate enema group (n = 57). Although there was no significant difference in failure rate between bowel preparations, efficacy was reported to be poor in a greater proportion following phosphate enema (12.3%) compared with the oral preparations (5.4%).

Conclusion: Of the bowel preparations currently used in this trust, the results indicate that if a single bowel preparation type is to be used this should be picolax for colonoscopy and klean-prep and senna for flexible sigmoidoscopy.

162 OESOPHAGEAL CANCER STAGING BY THE NURSE ENDOSONOGRAPHER

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Background: Opportunities to acquire the breadth of training acquired to meet the demands of diagnostic (oesophageal cancer) and interventional (lung cancer, pancreatic cystic lesions) EUS are few and hinder the expansion of EUS services. The central role of EUS to the staging of oesophageal cancers and the natural division between purely diagnostic and therapeutic endosonography raises the question of whether sub-specialisation is feasible and whether there might be a role for the nurse endoscopist (NE).

Aim: To conduct a prospective comparative study to assess the potential for a NE to stage oesophageal cancer with radial EUS.

Methods: One hundred patients (mean age: 64 years) with oesophageal cancer (proximal: 4, mid: 8, distal: 64, and distal/cardia: 24) underwent radial EUS. The studies were performed by a NE who had received prior hands on training in EUS (125 cases) and were observed by an experienced endosongrapher. Both independently reported a TNM stage in writing immediately following each case. All cases were performed under conscious sedation using an Olympus MH908 slim-probe.

Statistics: Agreement for T and N staging between the NE and the endosongrapher was measured using the kappa statistic. A kappa (κ) of 1 represents perfect agreement. Statistics were calculated on an intention to treat basis.

Results: The NE completed the full EUS procedure in 98 cases, requiring assistance in passing tightly strictured lesions in 2 cases. Assessing the accuracy of T-staging over 98 cases, there was very good

agreement (κ = 0.834) between both observers. When the first and second fifty cases were compared, agreement rose from good (κ = 0.79) to very good (κ = 0.89). Agreement for N-staging for this study was very good (κ = 0.858).

Conclusion: This study indicates the feasibility of extending the role of the NE to include radial EUS for oesophageal cancer staging. Such an approach would allow medically trained endoscopists to focus on interventional EUS.

163 PATIENT RECOLLECTION OF INFORMATION WITHIN AN ENDOSCOPY INFORMATION LEAFLET: IMPLICATIONS FOR INFORMED CONSENT

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Introduction: Endoscopy is an invasive procedure with associated morbidity and mortality. It is essential that patients are informed of these risks before undergoing the procedure. In common with many endoscopy units we send out an information leaflet to patients prior to the test. However, it is not known whether patients remember or indeed understand the information given in these leaflets and when giving consent.

Abstract 163

	Number of answers correct				
	4	3	2	1	0
Upper GI (%)	35	53	6	0	6
Lower GI (%)	37	27	30	6	0

Aims: The aim of this study was to determine what facts patients recalled from this information leaflet and the consent procedure.

Methods: The six page information booklet sent out describes the test, the preparation required, possible complications, and recommendations for action to be taken, if problems develop. Just before discharge and after their endoscopy, consecutive outpatients who had undergone gastroscopy or colonoscopy/flexible sigmoidoscopy were asked to complete four multi-choice questions with five stems, of which only one answer was correct. An example included ''the risk of making a small hole in the bowel during the test is: 1 in 10, 1 in 100, 1 in 1000, 1 in 10 000, or 1 in 100 000?'' The answers were within the information booklets.

Results: 50 patients (33 lower GI endoscopy, 14 male) completed the questionnaire. Only 35% having gastroscopy and 37% having lower GI endoscopy answered all 4 questions correctly (see table).

Conclusions: Patients fail to fully appreciate potential adverse events associated with endoscopic procedures. This is despite the distribution of detailed information prior to the procedure and could have medicolegal implications should complications arise.

164 OPTIMAL SITES TO BIOPSY FOR AN ACCURATE DIAGNOSIS OF *H PYLORI* INFECTION BASED ON ITS TOPOGRAPHICAL DISTRIBUTION USING CLO TEST: BODY *V* ANTRUM OF THE STOMACH

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Background: Accurate diagnosis of *H pylori* is critical for the optimal management of patients undergoing gastroscopy. Generally only one antral biopsy is taken for a CLO well. We have previously published that taking 3 biopsies (2 antral + 1 body = CLO3) in a CLO well is superior to histology for the detection of *H pylori*.[1] The sensitivity of CLO using biopsies from antrum *v* body remains unproven.

Aims: To assess the sensitivity of CLO test using 2 antral biopsies in a CLO well (CLO2A) *v* 2 body biopsies (CLO2B) in a CLO well using CLO3 as our gold standard.

Methods: We recruited consecutive patients over the age of 18 years undergoing a gastroscopy in a DGH requiring CLO testing, selection based on our previously published criteria.[1]

Results: 154 patients underwent CLO testing. 39 proved CLO +ve. All 39 patients were positive on CLO3, 38 on CLO2B, and 36 on CLO2A.

Abstract 164

	CLO2B+ve	CLO 2B −ve
CLO 2A +ve	35	01
CLO 2A −ve	03	114

Assuming the 100% sensitivity for CLO3, the sensitivity of CLO2B is 97.4% (95% CI 86.8% to 99.5%) and of CLO2A is 92.3% (95% CI 79.7% to 97.5%).

Summary and Conclusions: Using CLO well technique to diagnose *H pylori*, taking 2 biopsies from the body appears to be superior to taking 2 biopsies from the antrum of the stomach.

1. Vassalo J, Hale R, Ahluwalia NK. *Eur J Gastroenterol Hepatol* 2001;**13**:387–390.

165 AUDIT OF *H PYLORI* TESTING AT A UNIVERSITY HOSPITAL

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Background: Aintree University Hospital has a catchment area of 300 000. The endoscopy unit carried out 7148 gastroscopies, 30/06/02 to 01/07/03; 2637 (37%) of which were direct access. The diagnosis and eradication of *H pylori* infection plays a major part in the management of gastroduodenal diseases with WHO identifying *H pylori* as a grade 1 carcinogen. GPs expect their patients' *H pylori* status to be checked at endoscopy.

Aims: Identify current methods of *H pylori* detection, and the cost implications.

Methods: The histology report, 30/06/02 to 01/07/03, from a histopathology database, were retrospectively searched for gastric biopsies. The gastrointestinal physiology database was searched for 13C urea breath tests and the public health laboratory database for helicobacter serology requests over the same period.

Results: Histology is the biopsy based diagnostic method of choice at Aintree with 5087 (70%) patients in the given period having biopsies checked for *H pylori*. One block, sections cut at three levels and stained with haematoxylin and eosin, is used to identify *H pylori* (£30 pp). The diagnosis is usually made on routine HE stained sections but, where there is doubt, in addition, immunohistochemistry is carried out on approximately 10% of gastric biopsies (£20pp).

Carbon 13 urea breath tests (UBT, £11pp), primarily to determine whether eradication therapy has been successful, was the diagnostic tool for 331(6%). An in-house infrared isotope scanner is used to analyse samples generating same day results. Serum was sent to a recognised laboratory in a small number of cases (£4 p+p).

Conclusions: 94% of *H pylori* detection at Aintree is histology/biopsy based with cost implications for the laboratory. Should biopsy urease tests, CLO (£14 p+p), in selected patients, be reconsidered?

Abstract 165

TEST	POSITIVE	NEGATIVE	TOTAL	COST
Histology	1051 (26%)	4036 (74%)	5087	£162 784
13C Urea	100 (30%)	231 (70%)	331	£3641
Serology	3 (17%)	15 (83%)	18	£74
Grand Total	1154 (21%)	4282 (79%)	5436	£166 929

166 AN AUDIT OF IN-HOSPITAL ENDOSCOPIC WORKLOAD IN TWO UK TEACHING HOSPITALS

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Introduction: All endoscopic units are under increasing workload pressures. Part of this demand is for inpatient referrals. Delays in meeting this demand would not only result in delays in diagnosis and treatment, it is likely to cause delay in discharges.

Aims: We wanted to establish the demands posed by in-hospital endoscopy requests and its consequences over a 1 month period.

Method: The two teaching hospitals in Newcastle-upon-Tyne serve a local population of 270 000 and provide tertiary care for a region of approximately 4 000 000. All inpatient requests for an endoscopic examination (upper GI endoscopy, colonoscopy, flexible sigmoidoscopy, and ERCP) in the month of August 2002 were collected and retrospectively audited. Patient case notes were requested and the following data recorded patient demographics details, dates of admission, endoscopic request, and discharge, endoscopic findings. An estimate was made of the impact of the procedure to the timely discharge.

Results: 126 requests were made for inpatient endoscopic examinations during August 2002, 99 (78.5%) notes were retrieved and audited. 78 requests for upper GI endoscopy, 10 for colonoscopy, 8 for flexible sigmoidoscopy, 3 for ERCP. Inpatient endoscopic procedures represented 11.5% of the 1094 endoscopies performed during this month. There were 58 males and 41 females, with a mean age of 67 years. 74 patients were admitted for GI related problems. The delay from receipt of the request form to the procedure was a mean of 2.85 days. It was estimated that this delay contributed to 157 bed days. Where upper GI bleeding was the indication, the mean delay was 0.84 days.

Conclusion: Inpatient endoscopic requests represent a significant workload and not rapidly meeting this results in significant increase in bed days. Endoscopy units should be organised to meet this demand.

167 IS UPPER GASTROINTESTINAL ENDOSCOPY NECESSARY FOLLOWING A NORMAL BARIUM MEAL FOR EVALUATION OF DYSPHAGIA

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Background: In the initial evaluation of dysphagia, either barium meal or endoscopy can be used as the primary investigation. However, few studies have evaluated the role of endoscopy following a normal barium meal in those with dysphagia. The aim of our study was to see if endoscopy following a normal barium meal would provide additional information.

Methods: Consecutive patients investigated for dysphagia were identified from a prospective endoscopy database. The usual practice was to perform barium meal first followed by endoscopy (OGD). Patients were excluded if the OGD was done before the barium meal.

Results: A total of 80 patients were identified (37 male, 43 female, mean age 66 years). The mode for time of delay between barium meal and OGD was 1 month (range 3 weeks–12 months). Of these, 50 had barium meals reported as being normal. Discordant findings were seen in 26 (32%) of the combined investigations. In 5 patients OGD detected significant findings not seen on barium meal–oesophageal cancers (2), peptic oesophageal stricture (1), unexplained narrowing of the antrum (1), gastric ulcer plus pharyngeal pouch (1). In 2 patients, dysmotility diagnosed on barium meal was not detected at OGD. In 11 of these, the discrepancy was not felt to be clinically significant (OGD diagnosed hiatus hernia in 3 not seen on barium meal. Barium meal diagnosed dilated oesophagus in 3, hiatus hernia in 4, cricopharyngeal pouch in 1 not seen on OGD). In 8 patients, the discrepancy was beyond the sensitivity of the investigation (OGD diagnosed oesophagitis in 8 patients not seen on barium meal).

Conclusion: In patients complaining of dysphagia, discordance between barium meal and endoscopy occurred in 32%. Thus endoscopy and barium meal complement each other in the evaluation of dysphagia. Following barium meals reported as normal, endoscopy diagnosed an additional 10% (5/50) of clinically significant findings of which 4% (2/50) were cancers. Therefore, endoscopy is recommended after a ''normal'' barium meal for the evaluation of dysphagia.

168 ENDOSCOPIC SPHINCTEROTOMY FOR CHOLEDOCHOLITHIASIS IN PATIENTS YOUNGER THAN 50: LONG TERM FOLLOW UP STUDY

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Introduction: Despite the emerging indication of endoscopic sphincterotomy (ES) in young patients, little information is available about the long term (>10 years) effects of ES in these patients.

Method: Between 1984 and 1992, 38 patients (10 male, 32 female, age range 23–47) underwent endoscopic retrograde pancreatography (ERCP) and ES for choledocolithiasis. Early and long term complications were analysed, retrospectively.

Results: 38 patients underwent a total of 52 ERCPs for CBD stone and ES was successful in 37 patients. 17 patients had 20 ERCPs pre-cholecystectomy (mean time between ERCP and cholecystectomy 9.0 months, range 1 day–5 years) and 20 patients had 30 ERCPs post-cholecystectomy for CBD stone. 1 patient required one ERCP pre and post cholecystectomy for retained stones. Early complications (within 30 days) occurred in 5/52 ERCPs (9.5%), but there were no deaths. 4 patients (7.7%) had ES related bleeding, requiring blood transfusion in 3 patients and laparotomy in 2. One patient had a minor bleed requiring overnight observation. One patient developed cholangitis post ERCP (post-cholecystectomy group). Of the 10 patients who had more than one ERCP, seven were post-cholecystectomy. The common reasons for multiple ERCPs in this group were either failed cannulation or clearance of residual CBD stones. During long term follow up, 2 patients were lost to follow up, and 2 patients died of malignancy (1 of pancreatic cancer, 1 of somatostatinoma). 7 patients had slight abnormalities of liver function test or non-specific abdominal pain. There were no cases of recurrent stones, cholangitis, papillary stenosis, or cholangiocarcinoma.

Conclusion: ES in younger patients is a reasonable method of treatment for choledocholithiasis. It is safe in the long term. There was a high frequency of repeat procedures and complications in post-cholecystectomy ERCP group, suggesting that duct should be cleared either pre-operatively or at the time of cholecystectomy.

169 ENDOSCOPIC SPHINCTEROTOMY IS SUFFICIENT TREATMENT FOR MOST POST CHOLECYSTECTOMY BILE LEAKS

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Introduction: The endoscopic treatment of post operative bile leaks remains controversial, with some authors favouring stent placement and others endoscopic sphincterotomy.

Aims: To determine from a retrospective cohort review in what proportion of cases endoscopic sphincterotomy alone is an adequate treatment.

Patients and Methods: The hospital notes were reviewed of all cases of biliary leak undergoing endoscopic retrograde cholangiography (ERC), in our institution between 6.3.96 and 2.9.03. Thirty one cases of post-cholecystectomy bile leak were identified. In one case ERC could not be achieved. In 3 cases there was total bile duct occlusion, and in one case a bile duct stricture. These were excluded leaving a total of 26 cases for analysis. Operations performed were laparoscopic cholecystectomy (n = 9), laparoscopic cholecystectomy and conversion (n = 6), open cholecystectomy (n = 5), and open cholecystectomy and duct exploration (n = 2).

Results: Twenty two cases were treated by endoscopic sphincterotomy (ES) alone. The commonest source of bile leak was the cystic duct stump (n = 12), or the gallbladder bed (n = 4). Retained duct stones were removed in 4 cases. ES alone or combined with drainage of biloma was the only treatment needed in 20/22 (91%) cases. Median time from ES to cessation of drainage was 5 days, and median hospital stay 21 days.

Conclusion: Prompt endoscopic sphincterotomy is sufficient management for most cases of uncomplicated post cholecystectomy bile leak.

170 NEURAL NETWORKING TO PREDICT BLEEDING AT SPHINCTEROTOMY DURING ERCP

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Sphincterotomy at ERCP is perhaps the most dangerous of all procedures at therapeutic endoscopy. Neural networking is a computer based tool which we developed to improve the predictive power of clinical scenarios. We aimed to test this by building and training suitable neural networks and prospectively validating our predictions. Data from 65 patients who had undergone ERCP and sphincterotomy over the past year at our hospital were analysed to predict haemorrhage. Sphincterotomy was forwarded as a variable along with balloon sweep, use of an endoprosthesis, repeat ERCP, and age and gender of the patient. The table gives the weight (percentage effect) of each causal variable towards the other causal variables in order to achieve an effect. The accumulative effect is the strength with each variable pushes towards an effect.

This shows that basket sweep has an accumulative effect of 100% and when not used it decreases haemorrhage and when used we can be sure that we will get bleeding. It also means that the lower the sphincterotomy size the less likely it is that there will be bleeding. This is in absolute accordance with our clinical experience. We used student *t* test and Pearson correlations to compare with values obtained by neural

networking and highly significant correlations ($p<0.0001$) were obtained age and sex did not prove to have any correlations and were therefore not included in the table. These data could be used as a basis to build models as done here to make predictions in a case series of patients undergoing ERCP.

Abstract 170

Causal variable	Percentage effect	Accumulative effect
Repeat ERCP	38.78%	38.78%
Sphincterotomy size	23.04%	61.81%
Endoprosthesis	18.51%	80.33%
Balloon sweep	11.39%	91.72%
Basket sweep	8.28%	100%

171 REVIEW OF ERCP IN A SMALL UNIT

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Introduction: ERCP is increasingly performed not only in large centres but also in smaller units. ERCP reduces the need for surgery considerably, thus making it a cost effective procedure. Specialised large referral centres have a well proved success rate for selective cannulation and interventions but little is known about the viability of ERCP services in smaller centres.

Aims and Methods: We sought to review indications, success rates, and complications in patients undergoing ERCP at Prince Charles Hospital, a 490 bedded District General Hospital in South Wales. The case records of 380 patients undergoing ERCP between May 1997 and October 2002 were reviewed retrospectively, noting the indications for the procedure, source of referral, success rates of cannulation and intervention, and the complication rate. All ERCPs were performed by one endoscopist with several years' experience in ERCP.

Results: There were 147 (39%) male and 233 (61%) female patients. The age ranged from 13–97 years with a mean of 66 years. 71% were over 60 years. The overall cannulation rate was 87% and revealed biliary cholelithiasis in 169 (56%), bile duct strictures in 56 (19%) of which 32 (11%) were malignant. 3 patients had cancer of the head of pancreas and benign pancreatic disease, including chronic pancreatitis and pancreatic pseudocysts was present in 22 (8%). The procedure was normal in 67 (23%) patients. Therapeutic procedures were performed in 109 (38%) ERCPs. 31 patients (8%) developed mild–moderate pancreatitis, with 7 (2%) developing severe symptoms. There were no deaths directly related to the procedure during the period examined.

Conclusions: A cannulation success rate of 87% and an overall morbidity rate of 10% is in-line with larger units. There were no instances of either cholangitis or significant bleeding. Although the advent and increasing availability of MRCP will decrease the number of diagnostic ERCPs there is an increasing need for therapeutic ERCPs, especially in the elderly. This review demonstrates that a small unit with expertise concentrated in one endoscopist can provide a local service on a par with larger centres.

172 OUTPATIENT ENDOSCOPY—A FIVE YEAR EXPERIENCE

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Introduction: Castle Hill Hospital (CHH) endoscopy unit sees approximately 8500 patients per year for all endoscopy. There is no Accident and Emergency department within CHH and this reflects the absence of an acute upper gastrointestinal haemorrhage (GIH) service at CHH. Despite there being no acute upper GIH endoscopy service provided, general practitioners (GPs) can directly refer patients with haematemesis and melaena. There has been increasing interest in the safety of outpatient endoscopy for upper GIH. This review was to assess the CHH experience.

Method: Endoscopy records from January 1998 to October 2003 were reviewed. All patients included had been directly referred for upper GI endoscopy by their GP after an episode of haematemesis or melaena. Causes of upper GIH and 30 day mortality was recorded.

Results: There were 265 unselected outpatient referrals for upper GIH made to CHH. The 30 day mortality was 3.0% (8/265).

Abstract 172 Findings on endoscopy

No cause found	203
Oesophagitis	9
Gastric ulcer	5
Duodenal ulcer	12
Erosions	10
Tumours	3
VARICES	1
Polyps	2
Stomach lesion not identified	1
Mallory Weiss tear	2
Other	17

Conclusion: Outpatient endoscopy with strict patient selection is a safe alternative to admission for non-variceal upper GIH.

1. Cipolletta L, Bianco M, Rotondano G, *et al*. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomised controlled trial. *Gastrointestinal Endoscopy* 2002;**55**:1–5.
2. Almela P, Benages A, Peiro S, *et al*. Outpatient management of upper digestive hemorrhage not associated with portal hypertension: a large prospective cohort. *Am J Gastroenterol* 2001;**96**:2341–8.

173 HIGH MAGNIFICATION CHROMOSCOPIC POUCHOSCOPY: A NOVEL IN VIVO TECHNIQUE FOR SURVEILLANCE OF THE ANAL TRANSITION ZONE AND COLUMNAR CUFF FOLLOWING ILEAL POUCH ANAL ANASTOMOSIS

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Background: The residual rectal mucosa, anal transition zone (ATZ), and columnar cuff is a high risk zone for dysplasia. Conventional endoscopic assessment of the ATZ is difficult and often accompanied by biopsy sampling error. High magnification chromoscopic pouchoscopy (HMCP) may improve endoscopic surveillance and biopsy accuracy.

Methods: Patients with stapled J-pouches underwent HMCP using the Olympus CF240Z. Three discrete zones were identified:1) ATZ-appearing as a linear cellular matrix (LCM); 2) Columnar cuff-Kudo type I/II crypt; 3) Ileal pouch-villous projections. Each epithelial zonal interface was visualised as a matrix to type I crypt pattern and type I crypt to villous formation at the ATZ and the stapled ileal pouch-anal anastomosis, respectively. Quadrantic biopsies of each zone were then taken using HMCP guidance. The anticipated endoscopic pouch zone was compared to histology.

Results: See table.

Discussion: HMCP is a valid predictor of ATZ anatomy enabling accurate biopsy targeting of this high risk mitotic zone. The absence of dysplastic yield may reflect the low numbers of pouches >10 post operation years in this cohort. The identification of true columnar metaplasia and persistent severe villous atrophy using HMCP within the pouch reservoir may be useful when stratifying dysplastic risk and subsequent endoscopic surveillance intervals.

Abstract 173

HMCP appearance	n biopsies	Histology			
		Squamous	Columnar	Villous	Other
Zone 1 LCM	526	433	88	5	0
Zone 2 Kudo type I/II	531	42	388	99	2
Zone 3 Villous	529	6	38	482	3

n = 132. Median age 46 years (range 22–78), 71(54%) female, median pouch duration 6.5 years (range 2–12). Total no. of 'pouch years' surveyed = 231.
K coefficient of agreement between endoscopic zone 1 and squamous epithelium; zone 2 and columnar epithelium; and zone 3 with villous histology was 0.78, 0.69 and 0.85 respectively. Sensitivity 91%, specificity 87% and accuracy 93%. There were no cases of dysplasia at the ATZ.

174 EEG BISPECTRAL INDEX GUIDED SEDATION: BETTER, SAFER, FASTER

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Aims: Clinical assessment of depth of sedation is subjective and unreliable. The EEG based bispectral index (BIS) is used to guide sedation of paralysed patients on intensive care units. The aim of this study is to compare subjective assessment using the Ramsay sedation score (RSS) with objective BIS assessment of sedation and to validate the appropriate BIS range for procedural sedation.

Methods: 100 patients undergoing sedo-analgesia (midazolam and fentanyl) for ERCP and radiological GI procedures were divided into two groups. In group A (n=30) sedation was guided by the RSS with the operator blinded to the BIS recording. In group B (n=70) the operator titrated intravenous sedation to maintain a predetermined BIS level established from the results from group A. Recovery time, procedure duration, physiological parameters, and unplanned events were recorded in both groups.

Results: There was a significant correlation between the RSS and BIS ($p<0.001$). A BIS level of 85 corresponded to a RSS of 3. BIS levels between 80 and 90 were achieved in 37.5% in group A, but 74.7% in group B ($p<0.001$). Sedation approaching general anaesthesia (BIS <60) occurred in 5.5% of patients in group A but not in group B. Mean recovery time, duration of procedure, fentanyl, and midazolam doses were significantly reduced in group B. Unplanned events were also reduced from 27% to 17% ($p=0.29$).

Discussion: BIS monitoring enables more effective titration of sedatives to maintain a suitable level of consciousness for endoscopy and other procedures. The BIS offers a safe, reliable, and objective measure of sedation, without disturbing either patient or operator.

175 PATHOLOGY DETECTION AND PATIENT AGE IN OPEN ACCESS AND ''TARGET WAIT'' ENDOSCOPY—AN AUDIT

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Two week or target referrals for patients suspected to have a malignancy have been suggested to complicate endoscopy referral practices with little benefit to the patient and provide a back door for inappropriate referrals. In order to study this further, an audit was carried out over a 3 month period examining patients referred for open access and target wait endoscopy.

In a 3 month period, 19 target referrals and 79 open access referrals were received. Of the open access referrals 24 were requested as urgent and 75 contained sufficient information to be booked for endoscopy. Of the target referrals, 2 were judged to be inappropriate on pre-determined criteria. The table describes the key features of the two groups.

Conclusions: Target wait referrals had a lower DNA rate and higher pathology detection rate than either all patients referred for open access endoscopy or those referred urgently into the endoscopy service. None of the patients referred to the open access service who was under 50 years old (half of all referrals) had a significant pathology at endoscopy. It may, therefore, be more efficient to triage these to outpatient slots unless they have a recognised alarm indication. Open access endoscopy continues to have high levels of failure of patients to attend, with implications for effective use of endoscopy time.

Abstract 175 Key differences in patients referred

	DNA rate	Mean age (years)	Significant pathology	Significant pathology <50 years	Wait for endoscopy
Target wait (17)	12%	**68***	**23%****	6% (gastric ulcer)	11 (2–41) days
Open Access (all) (75)	27%	**49***	**5%****	0%	64 (6–140) days
Urgent OA (24)	37%	**49***	**4%****	0%	21 (6–53) days

*$p<0.001$ (Students t test). **$p=0.01$ (Chi^2 test)

176 WITHDRAWAL OF CONSENT DURING COLONOSCOPY

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Background: There is considerable debate regarding the definition of withdrawal of consent (WOC) and little data on its occurrence. As part of a prospective study on assessment of patient pain during colonoscopy, we collected data on WOC.

Methods: Data were complete in 467/474 procedures. Temporary WOC was assumed when a patient clearly stated that the procedure be stopped. If after explanation, additional sedation and/or analgesia, the patient again indicated that the procedure be stopped, this was considered true WOC and the endoscopist withdrew the colonoscope. Predicted and perceived pain scores were recorded by patients on a visual analogue scale. The frequency of true and temporary WOC, the relationship of its occurrence to patients' predicted and perceived pain, as well as the influence of gender and findings at colonoscopy to WOC were determined.

Results: Temporary WOC occurred in 7% and true WOC leading to the procedure being stopped in 1.9%. The occurrence of temporary and true WOC was not significantly related to the patients' predicted or perceived pain ($p=0.30$ and 0.39, respectively). About 50% of patients who asked for their procedure to be stopped correctly recalled doing so. More females than males (15:8) recalled asking for their procedure to be stopped. 66% of these patients had abnormal colonoscopy. 1.7% (8/474) of patients recalled asking for the procedure to be stopped ''inappropriately'' (that is, despite documentation that they had not asked to do so during their colonoscopy). M:F ratio was 5:3, 75% of these patients had abnormal colonoscopy and there was no statistical significance between the predicted and perceived pain scores ($p=0.97$) in this group.

Conclusions: True WOC resulting in procedure to be stopped is rare. Predicted or perceived pain from colonoscopy does not influence the occurrence or recollection of WOC. Approximately 2% of patients who recalled asking for their procedure to be stopped did so ''inappropriately''. This could lead to possible unfounded complaints. In those who recalled WOC (both appropriately and inappropriately), there were proportionately more females and more patients with abnormal findings at colonoscopy.

177 EXPERIENCE OF COLONOSCOPY IN PATIENTS AGED 85 YEARS AND ABOVE IN A DISTRICT GENERAL HOSPITAL

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Introduction: The UK has an ageing population; the over 85s are the fastest growing age group. Gastrointestinal disorders including colonic tumours are more common with advancing age. There is little information of the benefits of colonoscopy in the very old. The aim of this study is to evaluate the use of colonoscopy in patients aged 85 years or more.

Methodology: We carried out a retrospective study on all patients aged at least 85 years who underwent colonoscopy over a 5 year period. Data were obtained from case notes and our computerised endoscopy database. Demographic details along with the indications for examination, colonoscopic findings, complications, and completion rates were recorded.

Results: 316 out of 5094 (6%) colonoscopies were performed in patients aged 85 years and over. There were 203 women and 113 men with a median age of 87.5 years (range 85–100). The most common indications were anaemia (38%), rectal bleeding (22%), and diarrhoea (19%). Colonoscopy was completed in only 219 cases (69%). There were no perforations. The most common findings were diverticular disease (48%), colonic polyps (14%), and colonic cancers (9%). Normal findings occurred in 65 (30%) out of the 219 cases that had a complete examination. Colonoscopy revealed a diagnosis that could fully explain the patient's symptoms in 116 (37%) cases. Of those 30 patients with colonic cancer, 18 (60%) had a curative resection.

Discussion: Our study suggests that colonoscopy in the very old is safe but it may be technically more challenging as demonstrated by the lower completion rate. Difficulties with bowel preparation and higher incidence of diverticular disease in the elderly may contribute to the lower completion rate. The low incidence of complications and high yield colonic malignancies and polyps that were successfully resected reinforces the usefulness of colonoscopy even after 85 years of age.

Age alone should not be a excluding factor and there should be a low threshold for carrying out colonoscopy in this age group.

178 PROSPECTIVE AUDIT OF THE INCIDENCE OF PREPARATION COLITIS ASSOCIATED WITH SODIUM PHOSPHATE

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Introduction: Oral sodium phosphate (NaP) is a common and effective preparation for colonoscopy. However, it has been reported as causing transient mucosal ulcers of no clinical significance. This preparation associated colitis (PAC) may confuse clinical management if not recognised by the endoscopist, pathologist, and referring clinician.

Methods: The study was carried out in a district general hospital in England which routinely used NaP as bowel preparation for colonoscopy. A group of five experienced colonoscopists, educated in the endoscopic features of PAC, prospectively identified possible cases in consecutive endoscopies carried out over a three month period. The histology was then reviewed by a histopathologist and the clinical background obtained from the case notes.

Results: In the three month period 466 colonoscopies were carried out with 276 being performed by one of the study endoscopists (59%). Ten cases were prospectively identified as being consistent with PAC (3.6%). Histology from all cases was reviewed and reported as consistent with a pathological diagnosis of PAC. Case note review revealed one case where the clinical picture was consistent with a mild colitis which had improved on therapy. The other nine cases (3.3%) showed no clinical features consistent with a colitis. Furthermore, 2/9 patients had a flexible sigmoidoscopy with an enema preparation within one month of their colonoscopy and showed no features of PAC.

Conclusion: PAC occurs in more than 3% of people receiving NaP preparation for colonoscopy. This can confuse clinical management if not recognised. These findings support the use of alternative bowel preparations prior to colonoscopy and this is especially relevant in colonoscopies carried out for assessment of colitis. All endoscopists using NaP must be aware of the features of PAC.

179 A PROSPECTIVE, RANDOMISED COMPARISON OF BIPOLAR ELECTROCOAGULATION *V* CONVENTIONAL MONOPOLAR HOT BIOPSY FORCEPS IN THE ENDOSCOPIC TREATMENT OF DIMINUTIVE RECTAL ADENOMAS

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Background and Aims: To assess whether a cold biopsy from a diminutive rectal adenoma followed by destruction with bipolar (gold probe) electrocoagulation using large probes and high power setting would be a safe and efficient alternative to conventional monopolar hot biopsy forceps (MHBF). To the best of our knowledge, this is the only prospective randomised study that compares the technique of cold biopsy followed by bipolar electrocoagulation with that of MHBF.

Patients and Methods: Eligible patients were those undergoing colonoscopy, fulfilling the criteria of additional clearing colonoscopy and having at least one suspected rectal adenoma $\leqslant 5$ mm. At the time of endoscopy patients were randomised to receive treatment for their diminutive rectal polyps either with cold biopsy followed by repeated gold probe electrocoagulation (group A) using a 10 Fr catheter with setting 8 (40 W) for 1 second or with MHBF (group B). These patients were followed up with a colonoscopy at 2–4 months. Cases in which the histology of the removed diminutive rectal polyps was not neoplastic were excluded from the study group.

Results: A total number of 24 (15 males, 9 females, mean age: 56 years) patients were included in group A and 26 (14 males, 12 females, mean age: 61 years) in group B. At follow up colonoscopy residual adenoma tissue in the rectum was found in 2 patients of group A (8.3%) and in 4 of group B (15.3%) ($p>0.4$). No complications related to colonoscopy or endoscopic treatments in both groups occurred.

Conclusions: Our data suggest that the use of cold biopsy followed by bipolar electrocoagulation using large probes and high power setting for destroying diminutive rectal adenoma is at least similarly effective and safe as MHBF.

180 WILL WE FAIL TO DIAGNOSE YOUNGER PATIENTS WITH COLUMNAR LINED OESOPHAGUS BY FOLLOWING DYSPEPSIA GUIDELINES FOR ENDOSCOPY

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To assess whether strategies to reduce endoscopy in younger patients would significantly affect the diagnosis of columnar lined oesophagus (CLO), we have reviewed approximately 7200 endoscopy reports for 1966–7 and 2000–1. Patients included were newly diagnosed and had at least 3 cm of columnar epithelium. The symptoms of those aged less than 55 years were also noted. The number of patients with CLO in different age groups in each year is given in the table.

Abstract 180

	1996	1997	2000	2001
Total	24	42	62	66
Under 55	4(20%)	5(12%)	11(18%)	7(11%)
Under 45	2(8%)	3(7%)	2(3%)	3(4.5%)

Over the study period examinations increased by approximately 160% and the total number of CLO patients increased by 70% but the number of younger CLO patients remained static and small. Of 27 patients under 55 years, 11 (41%) had ''worrying symptoms'' likely to lead to endoscopy irrespective of age: bleeding 5, iron deficiency anaemia 3, persistent nausea 2, and dysphagia 1. On average 5 patients per year with simple dyspepsia and CLO would not be diagnosed by our service if stricter guidelines were applied. All but one of the under 55s diagnosed in 1966–7 were followed by endoscopy and histology to 2001 or 2002 with no evidence of progression from intestinal metaplasia to dysplasia. The introduction of stricter guidelines for endoscopy in younger patients will lead to some younger patients with simple dyspepsia and CLO remaining undiagnosed each year but there was no evidence in this study of an early progression to dyplasia in this group.

181 ARE 100 PROCEDURES ENOUGH TO ACHIEVE COMPETENCE IN COLONOSCOPY? PROSPECTIVE ASSESSMENT OF A TRAINEE'S ACQUISITION OF COMPETENCE, AND EVALUATION OF IMPACT OF TRAINING ON COLONOSCOPY SERVICE

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Introduction: Joint Advisory Group (JAG) guidelines suggest that trainees should achieve 90% caecal and 50% ileal intubation rates after a year of training and 100 colonoscopies. However, there is no objective evidence to support the validity of these figures. The study was designed to estimate the number of supervised procedures needed to achieve these intubation figures, and to assess the impact of having a trainee on scheduling of colonoscopy lists.

Methods: Data were collected prospectively on all colonoscopies involving a first year trainee and his chief trainer during a 12 month period. Close supervision was provided with verbal instructions as appropriate. Trainers took over if >20 minutes elapsed before reaching the proximal most end of the colon, or there was no progress for >5 minutes, or there was patient intolerance, or safety was threatened. Adjusted colonoscopy rate (ATCR) was calculated in sequential blocks of 20 with ATCR (excluding patients with previous colonic resection and unavoidable reasons for failure) as a function of the cumulative number of procedures. Data were also collected on insertion time, total procedure time, sedation, and complications.

Results: Of 185 colonocopies involving the trainee, 155 were supervised by a single trainer. ATCR ranged from 33% to 65% for the first 160 procedures, but rose to 86% during the last 25. The ileoscopy rate (IR) was 15%. During this period, the trainer performed 370 colonoscopies. Presence of the trainee had no impact on overall ATCR and IR (98.5 *v* 98.6% and 83.8 *v* 85.2%). The median anus to caecum and total procedure times were longer for procedures involving the trainee (15 *v* 7, and 27 *v* 16 minutes; 95% CI 6.5 to 9 and 7.5 to 11 minutes, respectively, $p<0.0001$). Assuming a 15 minute interval

between patients, presence of the trainee leads to over 25% decrease in the number of colonoscopies possible on a given list.

Conclusions: JAG guidelines seriously underestimate the number of procedures required to reach minimum competence threshold. Colonoscopy list size should be reduced by at least a quarter to incorporate a trainee. Colonoscopy training is expensive and should be factored in the planning of endoscopy services.

182 CAN WE MODIFY EXISTING AUTOMATIC SPEECH RECOGNITION TECHNOLOGY TO RELIABLY AND SAFELY MONITOR RESPIRATION IN PATIENTS SEDATED WITH PROPOFOL?

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Background: It is recommended that a) patients receiving propofol for sedation ''should receive care consistent with that required for deep sedation'' and b) the use of capnography (as an early warning sign of drug induced hypoventilation or apnoea) be considered (*Anesthesiology* 2002;**96**:1004–1017). The accurate continuous measurement of CO_2 concentrations in the breath of sedated patients without an ET tube in situ can, however, be problematic as indeed can monitoring transcutaneous CO_2 tension.

Aims: To develop a computerised method of auscultation which would a) allow continuous real time monitoring of respiratory rate and b) alarm when hypoventilation occurred.

Methods: The signal from the patient's breath sounds was used to build Hidden Markov Models (HMMs) of the different phases of respiration. HMMs model a type of stochastic process, and have been highly successful in automatic speech recognition for modelling the acoustic patterns of speech, which vary in both time and frequency (Cox S 1990. *In speech and language processing*. Chapman and Hall). The recorded breathing data were divided into a set for training the models and a set for testing.

Results and Conclusions: Even using a crude throat microphone positioned over the trachea and a relatively small training set of data, the result achieved on the testing set was an accuracy of almost 80% in recognising the different phases of respiration. Preliminary results using a more sensitive microphone to pick up both breath and heart sounds have been even more encouraging. Our preliminary results suggest that ''computerised auscultation'' may well provide a viable, non invasive, and inexpensive alternative to capnography in patients being sedated with propofol.

183 BASIC COLONOSCOPY: HOKEN COLON MODEL OR COMPUTER SIMULATOR FOR TEACHING TORQUE STEERING SKILLS

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Background and Aims: The Royal College of Surgeons' (RCS) basic colonoscopy skills course organisers recommend the use a Hoken Colon Model (HCM) in preference to either a Symbionix computer simulator (SCS) or the Immersion system (IS) for a) teaching basic torque steering, as well as b) both recognising and reducing sigmoid loops. They claim the HCM is more realistic than either the SCS or IS and we wished to see if this decision was really justified.

Methods: An experienced endoscopist (JH) performed 10 colonoscopies in patients while wearing a special pressure sensor glove on his right hand (see *Gut* 2000;**44**(suppl)A30). We recorded the mean pressures exerted on the 20 calibrated piezo resistive sensors in the glove during the first 5 minutes of each examination. Similar 5 minute pressure glove studies were then performed by JH using a) the HCM, b) SCS, and c) IS. In all cases JH tried to use the torque steering technique as taught on the RCS courses. We then calculated the mean cumulative forces generated by his right hand when colonoscoping patients and compared these values to those obtained in the other 3 groups.

Results and Discussion: Colonoscoping the two interactive computer simulators generated considerably smaller torque forces than occurred in the patient group ($p<0.001$) while the results with the HCM were much nearing to the real thing (patients>HCM>SCS>IS). Thus the mechanical model generates the most realistic range of torque forces needed to intubate the left side of the colon and justifies the RCS using the HCM in preference to the two much more expensive currently available computer simulators. The haptic feedback from both the SCS and IS will need to improve considerably if they are to reach their full potential.

184 PROSPECTIVE EVALUATION OF A PRE-ENDOSCOPY SCORING SYSTEM TO AVOID ADMISSION AND INPATIENT ENDOSCOPY IN LOW RISK PATIENTS WITH UPPER GI BLEEDING

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Introduction and Aim: Acute upper GI bleeding accounts for approximately 10% of acute hospital admissions. It is usual practice to admit all such patients for observation and inpatient endoscopy. The Blatchford scoring system (*Lancet* 2000;**356**:1318–21) used retrospective clinical and laboratory data to identify a low risk group prior to endoscopy, who did not require hospital based intervention (tranfusion or endoscopic haemostasis). We prospectively evaluated this scoring system in our hospital.

Methods: Over a six month period in 2002 all patients with upper GI bleeding presenting to Glasgow Royal Infirmary were prospectively audited, including their Blatchford score on presentation. Following analysis of this data, we subsequently introduced and audited a Blatchford score based protocol in 2003 to identify low risk patients who were not admitted (unless required for other reasons) but offered outpatient endoscopy.

Results: Of 208 bleeders during the 6 month audit period in 2002, 34 (16%) met the criteria for low risk Blatchford score, 26 (76%) of whom were admitted. Despite a median inpatient stay of two days (range 0–14 days), no patient from this group required hospital based intervention and none died. Following introduction of the Blatchford score based protocol in 2003, of the first 199 patients studied, 48 (24%) met the low risk criteria. Of these 48 patients, 42 were not admitted and none of the admitted patients had inpatient endoscopy. Only two patients failed to attend for outpatient endoscopy, but telephone follow up ensured no adverse outcomes. Of the 46 outpatient procedures, none required endoscopic therapy. Endoscopic findings were normal in 37 (80%), oesophagitis +/− Barrett's or gastritis/duodenitis in 8 (17%), and intestinal metaplasia in one. There were no ulcers, varices, or upper GI malignancies seen in this low risk group.

Conclusion: Implementation of the Blatchford pre-endoscopy score led to the avoidance of admission of over 20% of all patients presenting with upper GI bleeding, with no adverse patient effects. This strategy reduces hospital costs and allows inpatient endoscopy resources to be targeted more appropriately.

185 POLYPS—''LIGATE AND LET GO''

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Colonic polypectomy is associated with risk of bleeding and perforation. In selected patients, an alternative method of polypectomy that reduces this risk would be welcome.

Technique: In this a suitable pedunculated polyp is biopsied for histology. The pedicle is then ligated using an endoclip and left insitu. The adjacent mucosa is marked using Indian ink. At follow up endoscopy, two weeks later, original histology is reviewed and the marked site re–checked to ensure polypectomy is complete.

Patient 1: A 56 year old female presented to casualty with three day history of bloody diarrhoea and cramping abdominal pain. An inpatient diagnosis of infective diarrhoea was made and she commenced oral antibiotics. She settled and was discharged. At outpatient flexible sigmoidoscopy a single 8 mm pedunculated polyp in the distal sigmoid was found. The polyp was biopsied and the pedicle ligated using a single endoclip. The patient returned for follow up colonoscopy two weeks later, which confirmed complete expulsion of the polyp and all biopsies were negative.

Patient 2: A 70 year old man was referred for investigation of anaemia and altered bowel habit. Upper GI endoscopy was normal. A colonoscopy was performed and two polyps (largest 10 mm) were excised from the distal sigmoid. The procedure was abandoned early due to excess bradycardia. At repeat colonoscopy a further 8 mm pedunculated polyp was noted in the distal sigmoid. The pedicle was ligated using a single endoclip. Follow up flexible sigmoidoscopy

2 weeks later confirmed complete expulsion of the polyp and biopsy of the base showed normal mucosa.

Discussion: The advantages related to the method described here are several—it is safe and the risk of bleeding and perforation are minimised as the ligated polyp sloughs off in a more natural way. The main disadvantage is that histology of the entire polyp is not available. Further evaluation of this under-utilised technique is required to help gastroenterologists minimise risk for their patients during polypectomy.

186 YIELD FROM INVESTIGATING IRON DEFICIENCY ANAEMIA IN THE UNDER 45s: IS THE JUICE WORTH THE SQUEEZE?

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The British Society of Gastroenterology (BSG) recommends upper and lower gastrointestinal (GI) tract investigation in all men and postmenopausal women with iron deficiency anaemia (IDA), with anti-endomysial antibodies (EMA) in pre-menopausal women. There is no literature on the yield of this strategy in the young age group.

Methods: We performed a retrospective search of our endoscopy database (Sept 1999 to Mar 2003) for all patients endoscoped for anaemia <45 years old. Iron deficiency was defined as either a low ferritin, or low MCV with low iron and/or high TIBC.

Results: 147/159 (92%) notes of eligible patients were retrieved (61males: 86 females). 33 males met the criteria for iron deficiency. All 33 had a gastroscopy. Twenty two duodenal biopsies and a further 2 EMAs were negative. Six had abnormalities at gastroscopy (1 known cirrhotic had varices, 1 portal hypertensive gastropathy (PHG), 3 peptic ulcers (1 with abdominal pain and previous gastrectomy, and 1 gastric carcinoma). Thus investigation of IDA per se revealed important attributable pathology in 4 of 33 (12%). Sixteen of 33 had a colonoscopy showing colitis in 4, but one of these had bloody diarrhoea. Thus, important attributable pathology was found in 3 out of 16 (19%). Of the 86 females, 45 had confirmed iron deficiency. 44 out of 45 had a gastroscopy (1 refused). Thirty two duodenal biopsies and a further 3 EMAs were all negative. Four had abnormalities at gastroscopy (Barrett's oesophagus, a 0.5 cm gastric ulcer, gastric angiodysplasia, and PHG with varices (admitted with decompensated liver disease and melaena). Thus investigation of IDA per se revealed important attributable pathology in 3 out of 44 (7%). 24 of 45 had a colonoscopy, and a further 3 had barium enemas. Two patients had tubulovillous adenomas (<1 cm), 2 Crohns colitis (1 known Crohns), and 1 indeterminate colitis (but previous rectal bleeding and abnormal rigid sigmoidoscopy). Thus important new pathology was discovered in 3 out of 27 (11%) with complete lower GI tract examination.

Conclusions: Significant important pathology is found in young males with IDA. Our retrospective study suggests similar findings in menstruating females.

187 MANOMETRIC VISUALISATION OF LOWER OESOPHAGEAL SPHINCTER (LOS) AT FLEXIBLE ENDOSCOPY

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Introduction: Identification of LOS by visual inspection at endoscopy is unreliable and often impossible. Knowledge of the sphincter position detected by station pull through manometry (SPM) can not be effectively utilised for endoscopic therapeutic procedures as SPM is normally carried out by nasal intubation.

Aim: The aim of this study was to investigate the feasibility of LOS identification at endoscopy.

Methods: A specially designed four channel manometry catheter (LOS Locator) was inserted through the instrument channel of a flexible endoscope to identify and measure the LOS. A pull through technique was employed with 1 cm increments to identify LOS. SPM was carried out following endoscopic manometry (EM).

Results: SPM and EM were attempted on 12 patients and were successful in 9. One patient refused SPM. Neither SPM nor EM could be done in another because of recorder failure. In a third patient LOS could not be identified in EM trace. There were no complications related to the procedure. There was no significant difference between measurements made by SPM and EM with respect to LOS length (LOSL) and pressure (LOSP). LOSL and LOSP measured by EM revealed good agreement with paired SPM data (95% limits of agreement: LOSL −1.09 to 1.31 cm; LOSP −8.12 to 8.12 mm Hg).

Conclusion: EM is a valid and reliable technique which can be carried out safely and quickly. Identification of LOS at flexible endoscopy may have potential diagnostic and therapeutic applications. For example, it may allow therapeutic maneuvers directed to the LOS (for example, dilatation, Botox injection) to be carried out much more precisely or placement of catheter mounted or capsular pH probe 5 cm above the LOS.

188 HOW WILL BSG POLYP FOLLOW UP GUIDELINES AFFECT US?

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Aim: To assess whether our unit adhered to, and the potential impact of, the 2002 BSG Adenoma Surveillance Guidelines.

Method: A retrospective study of polyp follow up at our DGH, from 1/4-30/6/03. Data were obtained for all patients with colonoscopic polyps from the endoscopy, histology and hospital booking computers. Actual follow up details were compared with BSG guidelines.

Results: 79 of 528 patients had polyps (49 male, 30 female). Median age was 65 years (range 32–85). 130 polyps were detected (median 1, max 10; median size 4 mm, range 1–50 mm), of which 65 were histologically confirmed adenomas: 45 tubular, 18 tubulovillous, and 2 villous). 69% were in the rectum/sigmoid. 32 patients were low risk according to BSG guidelines: 16 had appropriate follow up (10 no follow up, 6* with 5 year follow up), and 16* had too short a follow up (mean 27 months, range 12–36). 13 patients were intermediate risk: 3 had the correct 3 year follow up, 6 had too short a follow up (mean 9 months, range 6–24), 1 too long a follow up (5 years) and 3 had no follow up. 1 patient was high risk, warranting 1 year follow up, but received 3 year follow up. 11 patients *had incomplete polyp clearance*: 4 received appropriately rapid follow up, 2 received late follow up (both 9 months), and 5 received no follow up. Of the 22 patients with non-adenomatous polyps only, 8* had an unnecessary follow up colonoscopy booked. In total, 37 (47%) received appropriate follow up, but 30 (38%) were given too short a follow up interval (including 8 who did not require follow up) and 12 (15%) too long a follow up interval (including 8 who received no follow up). During the 3 month study, 47 follow up appointments were made—adherence to BSG guidelines would have added 8 apparently overlooked follow up appointments, but could have saved up to 30 other follow up procedures*, resulting in a 47% reduction in follow up colonoscopies.

Conclusion: This study demonstrates the need to develop a more robust adenoma follow up booking procedure, to prevent inappropriate recalls (exposing patients to unnecessary risk) and to prevent patients being lost to follow up (with consequent risk of developing colorectal cancer). Adherence to BSG guidelines would considerably reduce both the number and the frequency of follow up surveillance colonoscopies, allowing more appropriate allocation of endoscopic resources.

189 SUPPLEMENTAL OXYGEN DURING THE RECOVERY PERIOD FOLLOWING ENDOSCOPY REDUCES DESATURATION

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BSG guidelines recommend that at risk patients be given oxygen enriched air while undergoing endoscopic procedures, but not in the recovery period. While supplemental oxygen has become standard practice in our unit for all patients having sedation, we identified that this was not the case in the recovery area and one to one nursing care was also no longer available. We performed an audit to assess the frequency of desaturation episodes (pulse oximetry <90%) within the recovery period and also to determine if factors such as ASA grading, complexity of the procedure performed, or sedative combinations used would predict those patients most at risk from desaturation post endoscopy.

100 patients requesting sedation and attending for a range of endoscopic procedures (gastroscopy (OGD), colonoscopy (C), combined endoscopy (OGD + C) and ERCP) on the lists of 2 consultants with differing sedation practices were included in the study. The rate of oxygen desaturation was 20% for the whole group. Although increasing ASA grading, procedural complexity, and combination sedation regimes (opiates with benzodiazepines) were observed to confer an increased likelihood of desaturation episodes, there were in fact no group of patients that could be considered not at risk.

ASA I = 18% (12/67), ASA II = 25% (7/28), ASA III = 20% (1/5); OGD = 15% (7/45), C = 24% (9/37), OGD+C = 25% (2/8); ERCP = 22%

(2/9); Benzodiazepine alone 15% (7/45), opiate + benzodiazepine 24%; (13/54).

The use of supplemental oxygen in the recovery period, until the patient is fully ambulant, became standard practice within our unit and the audit was repeated with a further 100 patients. There was a similar case mix and sedation practices had not altered, however, desaturation episodes occurred in just 3%. Desaturation in recovery is now unusual in our unit.

190 OLDER AGE, FEMALE SEX, AND TRAINEE ENDOSCOPIST ARE FACTORS ASSOCIATED WITH LONGER INSERTION TIME AT COLONOSCOPY

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Introduction: Ability to predict factors associated with difficult colonoscopy may help in patient selection and efficient scheduling of endoscopy lists.

Methods: Procedure completion rate is not a useful marker for difficult colonosocpy as expert colonoscopists achieve very high caecal intubation rates. Insertion time may, however, serve as a useful index of technical difficulty. Data were collected prospectively on all consecutive colonoscopies from May 2002 to October 2003 on insertion time defined as the time taken to reach the proximal most end of the colon (caecum or anastomosis in case of previous surgery). Data relating to patient demography, seniority of the endoscopist, and the type of colonoscope were recorded. Insertion times longer than the median (10 minutes) were coded as long. The predictor variables were dichotomous with age over 65 years being classified as old, and a body mass index of >25 coded as obese. Logistic regression analysis was used with insertion time as the dependant variable with the following predictor variables: age, sex, BMI, severe constipation, history of previous colonic resection, previous pelvic surgery, diabetes mellitus, use of antidepressants or anticonvulsants, the endoscopist (consultant *v* trainee) and the type of colonoscope (variable stiffness *v* standard).

Results: Thirty seven procedures were excluded from analysis (28 for unavoidable failure to reach ceacum and 9 due to avoidable failure). Some others had to be excluded due to missing data points. There were 579 analysable procedures. 243 of them were in men and 336 in women. The median age was 62 years (range 14–93). 346 procedures were performed by a consultant and 233 by trainees independently or assisted by the consultant. The median insertion time was 10 minutes (interquartile range 6.5 to 16.5 minutes). The adjusted total colonoscopy rate was 98.5%. The ileoscopy rate was 86%. The following factors were associated with a longer insertion time: trainee colonoscopist, age over 65 years, and female sex ($p<0.0001$, 0.017, and 0.025 respectively).

Conclusions: Endoscopy list scheduling should take into account patient factors such as age and sex, and whether the procedure is to be performed by a trainee endoscopist.

191 POLYETHYLENE GLYCOL (KLEAN-PREP) PROVIDES BETTER BOWEL PREPARATION FOR COLONOSCOPY THAN MAGNESIUM OXIDE PLUS SODIUM PICOSULPHATE (PICOLAX)

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Introduction: Good bowel preparation prior to colonoscopy is essential if significant lesions are not to be missed and in order to achieve high completion rates. Previous studies comparing different types of bowel preparation have been small and have given conflicting results as to the superiority of one method over another.

Methods: A retrospective study was carried out of all colonoscopies performed in two university teaching hospitals over a period of one year. The data were collected prospectively and entered into two databases (''Infoflex'' and ''Endoscribe''). At the Royal Hallamshire Hospital (RHH) the predominant bowel preparation was Picolax, at the Northern General Hospital (NGH) it was Klean-Prep. The primary outcome measure was the proportion of colonoscopies where the bowel preparation was graded as poor.

Results: 1847 colonoscopies were carried out at the NGH. Of these, in 1763 cases the patient received Klean-Prep. At the RHH, 1822 colonoscopies were carried out and 1490 patients were given Picolax. Of the Klean-Prep patients at the NGH the bowel preparation was classified as poor in 238 cases (13.5%). For patients given Picolax at the RHH the preparation was graded as poor in 258 cases (17.3%). This difference was statistically significant ($p<0.003$), when analysed using χ^2. Normal procedures were more likely to be reported when Picolax was used as the bowel preparation ($p<0.001$). Fewer tumours and polyps were seen in those given Picolax but the differences did not reach statistical significance ($p=0.16$ and $p=0.10$, respectively).

Conclusions: Picolax is significantly more likely than Klean-Prep to produce bowel preparation graded by the endoscopist as poor. In addition, the greater proportion of normal procedures reported with Picolax may be due to subtle, potentially serious lesions being missed due to inadequate bowel preparation.

192 LOW COLONOSCOPY COMPLETION RATES ARE UNLIKELY TO BE EXPLAINED BY INDICATION ALONE

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Introduction: Previously the BSG carried out a national audit showing a worryingly low colonoscopy completion rate of less than 80%. It has been suggested that in the UK at least, part of this low completion rate may be related to the colonoscopist's perceived need to reach caecum.[1] For example, caecal intubation may be less important in a patient with rectal bleeding than in a patient with anaemia.

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Indication for colonoscopy	Number completed (%)	p Value
Overall total	1481/1812 (81.7)	–
Rectal bleeding	437/547 (80.2)	ns
Abdominal pain	391/479 (81.6)	ns
Change in bowel habit	568/702 (80.9)	ns
Anaemia	210/286 (73.4)	<0.001
IBD assessment	78/93 (83.8)	ns
Weight loss	112/156 (71.8)	<0.005
Surveillance	381/426 (89.4)	<0.001

Methods: A prospective study was carried out of all colonoscopies performed on a joint medical and surgical list from October 2001 to September 2002. Using the ''Infoflex'' database, indication for endoscopy and colonoscopy completion rates were both recorded and analysed.

Results: 1812 colonoscopies were carried out. In 1481 colonoscopies the caecum was said to have been reached giving an overall completion rate of 82%. The likelihood of completion for certain indications did vary significantly from the overall mean when analysed using χ^2 (see table), although not in the expected manner.

Conclusions: Although it is reassuring that the colonoscopy completion rate is very nearly 90% in procedures done for surveillance, it is worrying that caecal intubation in fact occurs less frequently than expected in cases where the indication is anaemia or weight loss. The excuse that low completion rates may be explained by a lack of clinical necessity should be dismissed.

1. Robinson J, Small P, Bell GD, *et al.* A prospective audit of colonoscopy in a large DGH—factors affecting caecal intubation rates [abstract]. *Gut* 2001;**48**:A10.

193 BILIARY MANOMETRY IN SPHINCTER OF ODDI DYSFUNCTION: WHEN IS IT JUSTIFIED?

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Introduction: Sphincter of Oddi dysfunction (SOD) is a disease characterised by biliary or pancreatic type pain often in post-cholecystectomy patients. Endoscopic sphincterotomy (ES) of the biliary and/or the pancreatic part of the sphincter is highly effective in those with dilated ducts and abnormal liver function tests (Geenen type 1). Without the presence of these two criteria (Geenen types 2 and 3) results have been disappointing.

Aim and Methods: To evaluate prospectively the efficacy of ES in Geenen types 2 and 3 confirmed by biliary manometry.

Results: From Aug 1998 to Nov 2002 we performed biliary manometry in 34 patients. 18 had type 2 and 16 had type 3 SOD dysfunction. Of these, increased pressures were found in 12 type 2 and 11 type 3 patients. Three were men and 20 women, mean age 42 (range 21–66). Twelve patients had an MRCP (with secretin and cholecystokinin injection) performed before biliary manometry to search for evidence of SOD and other pathology. Sixteen patients had increased biliary pressures (mean 61.3 mm Hg) and 15 patients increased pancreatic pressures (mean 54.1 mm Hg). We were unable

to cannulate the pancreatic duct in 4 and the common bile duct in 2 patients. From the 17 patients in whom both the common bile duct and the pancreatic duct were cannulated, the pressures were raised in both parts of the sphincter in 8, in the pancreatic part only in 5, and in the biliary part in 4 patients. Biliary ES was performed in all 23 patients and pancreatic ES in 16. A pancreatic stent was inserted in 16 patients. Mean follow up was 15 months (range 6–48 months). At the end of follow up 6 of the 12 type II SOD patients and 3 of the 11 type III had significant improvement in their pain. Three patients developed moderate pancreatitis following the procedure which resolved without sequellae. MRCP failed to diagnose accurately the presence of SOD.

Conclusions: Biliary manometry and ES was safe in our group of patients. However, in view of the low efficacy it may not be indicated in patients with type 3 SOD.

194 LONG INSERTION TIME AND FEMALE SEX ARE ASSOCIATED WITH GREATER PAIN PERCEPTION DURING COLONOSCOPY

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Introduction: Factors affecting perception of pain during colonoscopy are poorly understood. Ability to predict such factors may help improve patient satisfaction with the procedure.

Methods: Data were collected prospectively on all consecutive colonoscopies between April 2002 and November 2003. After procedure, patients were asked to score any pain experienced during the procedure on a visual analogue scale of 0 to 100. Data on a number of putative variables likely to have an effect on pain perception were recorded. These included patient factors (age, sex, and alcohol intake); experience of the endoscopist (consultant *v* trainee); level of sedation given; and insertion time defined as the time taken to reach the proximal most end of the colon (caecum or anastomosis in case of previous surgery). Age was categorised as over 65 years or younger. Alcohol intake was categorised as high (>21 units/week) or low. Sedation was ranked as 1 if the dose of midazolam was 1 mg or less and/or the dose of pethidine was 12.5 mg or less. If the dose of midazolam was 5 mg or more and/or the dose of pethidine was 50 mg or more, that was graded as 3. All other combinations of doses were ranked as 2. For categorisation of insertion time, the median figure of 10 minutes was used as the cut off point to define a long insertion time. Multiple regression analysis was performed to test any association between pain score and putative categorical predictors defined above.

Results: Of the 650 procedures, 278 were in men and 372 in women. The median age was 63 years with an interquartile range (IR) of 46 to 74. 393 procedures were performed by one consultant and 257 by trainees independently or assisted by the consultant. The median insertion time was 10 minutes (IR 6.5 to 15.5). The median total procedure time was 20.5 minutes (IR 14.5 to 28). The adjusted total colonoscopy and ileoscopy rates were 98.5% and 86%, respectively. The median pain score was 50 (IR 30 to 70). Pain score was positively associated with insertion time longer than 10 minutes and female sex ($p<0.0001$ for both). No other variable had a significant association.

Conclusion: Long insertion time and female sex are associated with greater pain perception. Skilled rapid intubation may be more important than sedation in reducing pain, which is an important factor in improving acceptance of the procedure.

195 TECHNICAL OUTCOMES OF ERCP IN PAEDIATRIC PATIENTS

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Background: Data on the outcomes of ERCP in paediatric patients are limited due to fewer studies and small numbers of patients in published trials.

Aim: To determine if there is a difference between paediatric (<18 years) and adult patients with respect to success and complications of diagnostic and therapeutic ERCP.

Methods: This is a case controlled study of all paediatric patients who underwent ERCP at a single centre (1994–2002). Paediatric patients were matched with adults for all variables (indications, procedural complexity) except age and the outcomes with regard to technical success and complications were compared between both groups. Level of procedural complexity was defined as per criteria established by the ASGE committee on outcomes research. Complication severity was judged based on standard consensus criteria.

Results: Ninety two paediatric (mean age 10.3 years, SD 4.47) and 92 adult patients (mean age 58.1 years, SD 17.05) underwent 129 and 137 ERCP procedures, respectively. For each group, level I complexity included 55 patients, level II 10, and level III 27 patients. Procedural success rate was 99% in the paediatric *v* 98% in the adult population (p=ns). The complication rate was not significantly different between paediatric and adult patients (2.1% *v* 2.3%, p=ns). With the exception of a single adult patient who developed post-sphincterotomy bleeding after extraction of a large CBD stone (level II complexity), complications in both groups were encountered only in level III patients.

Conclusions: ERCP on paediatric patients in expert hands carry a high degree of success and low complication rate that is comparable with the adult population.

196 DATA MINING TECHNIQUES APPLIED TO AN ENDOSCOPY DATABASE: WHAT ADDITIONAL INFORMATION MIGHT IT GENERATE?

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Background: Large databases may contain interesting patterns in classification data that represent valuable information that could be used to supplement clinical decisions. However, due to the size and complexity of the data, it is often extremely difficult to identify these patterns from what is just random variation. We wished to test out some of the newer data mining techniques we have developed at UEA and applied them to the EndoScribe database on our local Endoscopy Unit.

Methods and Results: We used the EndoScribe database located in the Endoscopy Unit of the Norfolk and Norwich University Hospital. We selected one year's data, from May 2002 to April 2003. The database contained 10 530 records. After records with missing data were excluded, we had 2299 colonoscopies and 6217 OGDs. We elected to look particularly for any interesting patterns of behaviour among different endoscopists in the case of patients over the age of 70 years of age undergoing colonoscopy (n=735). We reasoned that a) most cardio-pulmonary complications tend to occur in this age group and b) all endoscopists know that the dose of sedation given to elderly patients should be reduced significantly. The group of 735 patients >70 years of age who underwent a colonoscopy were randomly dived into a training group (n=498) and a test group (n=237). With midazolam dosage as the target field and ''Datalamp'' as the data mining method employed, by far and away the greatest predictor of dose given was the individual endoscopist and not either the age of the patient or dose of pethidine co-administered.

Discussion: To our knowledge data mining techniques have not been previously applied to endoscopy databases. Our preliminary results, taking just one variable (midazolam dosage) in elderly and therefore at risk patients, suggest that there are many other useful ''nuggets'' out there waiting to be discovered.

197 WOULD RAISING THE AGE THRESHOLD FOR OPEN ACCESS ENDOSCOPY FROM 55 TO 65 YEARS LEAD TO A DELAY IN THE DIAGNOSIS OF OESOPHAGO-GASTRIC CANCER

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Introduction: One priority of open access endoscopy (OAE) is that patients with alarm features can be investigated without delay. Recent studies suggest that an age threshold of 55 years for OAE among patients without alarm features is appropriate. Could this age threshold for OAE be increased from 55 to 65 in patients with stable, non-alarm dyspepsia without cases of oesophagogastric cancer being subject to delay in diagnosis?

Methods: All patients aged 55–65 years who underwent OAE in a nurse endoscopist led clinic over 25 months were identified prospectively. The general practitioner referral proforma was analysed for patient symptoms, their duration, current therapy, and urgency of OAE request. These data were matched with procedure findings.

Results: (A) 1153 patients underwent OAE. 318 (147 male) were aged 55–65. 68 patients had alarm features: 34 dysphagia, 17 weight loss, 11 haematemesis/melaena, anaemia (1), vomiting (2), severe pain (1), and mass (2). Only 39 (57%) were referred urgently. The median time from referral date to OAE was 21 working days. (B) Five patients (1.6%) had cancer (two oesophagus; three gastric). Two had reflux symptoms only (non-urgent referrals); one had vomiting in association with reflux (urgent referral). Another had dysphagia (urgent referral), and the fifth had epigastric pain (non-urgent referral). 34% had gastro-oesophageal reflux disease (GORD: 88/318), or Barrett's oesophagus (19/318: only one patient had dysplasia (high grade) on biopsy);

23.5% (75/318) had gastroduodenitis; 3.7% (12/318) had benign gastroduodenal ulcer disease; 13.5% (43/318) had an hiatus hernia only, and 21% (67/318) had normal findings. Nine patients (2.7%) declined intubation. (C) None of the 29 patients, with alarm features who were not referred urgently, had cancer.

Conclusions: Three cancers were detected in patients who did not have alarm features, suggesting it would not be appropriate to increase the current OAE age threshold to 65 in patients without alarm features.

198 MANAGEMENT OF PROXIMAL BENIGN OESOPHAGEAL STRICTURES SECONDARY TO RADIOTHERAPY AND SURGERY FOR HEAD AND NECK CANCERS—CASE SERIES FROM A SINGLE CENTRE

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Background: Proximal benign oesophageal strictures (PBOS) occur in 10–58% of patients following treatment for head and neck cancers (HNC). There are few reports on the dilatation of these strictures and no randomised controlled trials to date.

Aim: To assess the efficacy and complications of dilating PBOS following radiotherapy and surgery for HNC.

Methods: Seven patients underwent dilatation of PBOS post HNC treatment between 1989 and 2003 at our institution. Clinical records were reviewed retrospectively.

Results: There were 5 males and 2 females. The mean age at diagnosis of HNC was 54 years (range 42–72 years). The mean follow up period was 60 months (range 12–56 months.) Two patients had laryngeal carcinoma and two had pyriform fossa carcinoma. In addition there was a case each of glottic, vocal cord, and pharyngeal carcinoma. All patients received radiotherapy and in two patients chemotherapy was given. The mean period of onset of dysphagia from the primary treatment was 70 weeks (range 0–284 weeks). The mean distance to the proximal end of the stricture was 14 cms (range 11–18 cms). The mean time to first treatment for stricture was 81 weeks (range 7–285 weeks). All strictures were benign (biopsy proven). Prior to referral to the gastroenterology department 5 patients underwent oesophageal dilatation in the ENT department under general anaesthesia. The procedure failed in two patients. The remaining patients underwent 27 procedures (median—3, range 1–12). The complication rate was 11% (1 bleeding, 1 mucosal tear, 1 creation of false passage). Following GI referral, three patients underwent a total of 16 endoscopic dilatations with Savary Gilliard dilators. The complication rate was 6% (1 sealed perforation). Subsequently all patients underwent repeated balloon dilations in the gastroenterology unit (mean number of dilatations per patient 54, range 1–110, total performed 375). Strictures were dilated at intervals from 1–8 weekly to maintain swallowing. The mean duration of dilation was 9 mins (range 2–10 min) per procedure. There was no morbidity or mortality noted following the 375 balloon dilations. Additional treatments included triamcinalone injections and stricture incision using sphincterotome in one patient and ileal interpositioning in one patient with refractory PBOS.

Conclusion: Endoscopic balloon dilation is a safe and effective treatment for PBOS following treatment of HNC. Future prospective studies of quality of life and dysphagia scores should be considered in assessing outcomes following treatment for PBOS.

199 MRCP AND ERCP FOR THE INVESTIGATION OF PANCREATICOBILIARY DISEASE

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Aims: to compare and contrast the use of MRCP and ERCP in pancreaticobiliary (PB) disease at our centre in consecutive patients over a 20 months period.

Methods: Between Oct 2001 and July 2003, all patients who had MRCP or ERCP for primary assessment of PB disease were identified using a computerised database. The records of these patients were analysed.

Results: Following an initial ultrasound, 119 patients had MRCP and 284 patients (354 procedures) had ERCP. 75% of ERCPs were therapeutic. Abdominal pain and abnormal liver enzymes were the main indications for MRCP. Jaundice or gallstones on US were the main indications for ERCP. 28/119 patients (23%) having initial MRCP subsequently had ERCP; in these patients agreement between the procedures using Kappa statistics were as follows: bile duct size 0.20 (poor), bile duct stone(s) 0.44 (moderate), gall bladder stone(s) 0.45, and pancreatic duct abnormality:1.0 (excellent).

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	MRCP		ERCP	
N (patients/procedures)	**119/119**		**282/354**	
Male:Female	**38:81 (1:2.1)**		**104:178(1:1.7)**	
Median age (range)	58 y (18–96 years)		68 y (22–95 years)	
Main indication:	n	%	n (proc)	%
Jaundice	5	4.2	78	22.0
Pain/colic	40	33.6	10	2.8
Pancreatitis	17	14.3	34	9.6
Cholangitis	0	0	27	7.6
Stone on US or CT	5	4.2	66	18.6
Abnormal LFTs	37	31.1	55	15.5
Follow up procedure	–	–	65	18.3
Other	15	12.6	19	5.4
Diagnosis	N	%	N (patient)	%
Normal	46	38.7	45	16.0
Gall bladder stone	31	26.0	35	12.4
Bile duct stone	21	17.7	96	34.0
Bile duct dilatation	6	5.0	32	11.4
Tumour:cholangio/ pancreatic	3	2.5	42	14.9
Failed procedure	1	0.8	16	5.7
Other	11	9.2	16	5.7

Conclusions: 30% of patients with suspected PB disease have initial MRCP rather than ERCP. They tend to be younger and are more likely to have abdominal pain +/− abnormal liver chemistry. Agreement between procedures is moderate at best for biliary disease and excellent for pancreatic disease. MRCP and ERCP are used synergistically at our centre the former reducing the burden on the latter.

200 COLONOSCOPY OR BARIUM ENEMA: BEST TEST OR PATIENT CHOICE

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Informed consent involves not only explaining a procedure and its possible complications, but also offering viable alternatives. Colonoscopy is a more accurate test compared with double contrast barium enema, and also affords therapeutic intervention. It does, however, usually require sedation and carries significantly greater risk of perforation compared to barium enema.

Methods: Consecutive patients requiring inspection of the colon were fully informed of the advantages and disadvantages of colonoscopy and barium enema and asked their preference. They were advised: colonoscopy is the most accurate test (95%) for detecting significant pathology, allows biopsy/poylpectomy, completion rate is 90% but there is a risk of perforation (1 in 1000/15000); Barium enema is less accurate (85%), diagnostic only, however, completion rate is >90% and it has negligible perforation risk (1 in 25000).

Results: 62 (30 male, 32 female) patients had fully informed consent. Median age 58 years (range 22–79). Indications (some patients had more than one symptom): diarrhoea (24), altered bowel habit (15), iron deficiency anaemia (15), PR bleeding (6), weight loss (7), pain (8), and encoparesis (1). 29% patients elected to have colonoscopy, with accuracy being the determining factor (15/18), 42% elected to have barium enema, mainly because of the negligible risk of perforation; 29% had no preference (and were advised to undergo colonoscopy (11/18) and barium enema (7/18) by the physician).

Conclusions: Although colonoscopy is a more accurate tool for investigating the colon, a significant proportion of patients preferred barium enema on account of its negligible risk of perforation. There was no patient preference in procedure between sex.

201 ACID PEPTIC DISEASE IN LONDON—ETHNIC DIFFERENCES AND TIME TRENDS

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Introdution: Gastro-oesophageal reflux disease (GORD) is uncommon in the east. In western countries, the prevalence of GORD has increased

over recent years while that of gastric ulcer (GU) and duodenal ulcer (DU) has decreased.

Aims: To determine the effect of ethnicity on prevalence of GORD, DU, and GU and to study the time trends in the prevalence of these conditions in patients presenting for upper gastrointestinal endoscopies (OGDs).

Method: All OGDs performed in a single hospital in London from Jan 1997 to Dec 2002 were studied. Indian sub-continent Asians (ISCA) were identified by name.

Table 1 Ethnicity and diagnosis 1997–2002

	Total	BO	RO	GU	DU
ISCA	1547	22	208	41	75
NA	14667	480	2256	512	635
P		<0.001	<0.05	NS	NS

Results: 16214 patients were included: 1547 ISCA and 14667 non-Asians (NA). The prevalence of Barrett's oesophagus (BO) increased from 1.5% in 1997 to 3.23% in 2002 ($p<0.0001$) in patients presenting for OGDs. There was no change in the prevalence of reflux oesophagitis (RO), GU, and DU. Effect of ethnicity is shown below.

Conclusions: ISCA were less likely than NA to have BO and RO but the prevalence of GU and DU was unaffected by ethnicity. The prevalence of BO has increased over the study period. In contrast, that of RO, GU, and DU remained unchanged.

202 COLONONSCOPY COMPLETION RATES: THE VALUE OF A CODED LEAGUE TABLE

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A recent BSG/intercollegiate audit of colonoscopy practice has highlighted the problem of low colonoscopy completion rates. We have therefore used our computerised reporting system, which requests all endoscopists to detail the extent of examination and document the landmarks identified, to generate a coded league table of individual, and departmental results.

All colonoscopists agreed to participate. Data were collected for an initial period of 6 months. A coded league table of completion rates was then circulated and each endoscopist was made aware of their own code confidentially. Data were collected for a further 3 months, without feedback, and again for a 3 month period the following year. Endoscopists performing fewer than 10 procedures during any study period were excluded from the main analysis.

During the initial period, 15 endoscopists performed 791 colonoscopies. Intention to treat, reported completion rates were 77 (37 to 90)% median (range), with 6 endoscopists reporting rates less than 75%. Following coded feedback, reported completion rates rose to 80 (72 to 96)% in 349 examinations, with only one reporting a rate less than 75%. Without further feedback, this improvement appears to have been maintained, with this year's rates being 86 (50 to 92)% in 446 examinations. Again, only one endoscopist reported a rate less than 75%. We have found this process a non-confrontational way to look at variability in endoscopy practice.

Conclusions: The publication of a coded league table of colononoscopy completion rates was associated with reported improvements, which appear sustained over time. Our departmental results are now approaching JAG guidelines, which suggest that trainees should achieve complete colonoscopy in over 90% of examinations. Further objective measures of quality assurance in colonoscopy could be introduced using a coded league table technique.

203 ENDOSCOPIC MUCOSAL RESECTION—A SAFE AND EFFECTIVE NON-SURGICAL OPTION IN THE MANAGEMENT OF COLORECTAL POLYPS

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Introduction and Aim: Colonoscopic polypectomy plays a major role in preventing colorectal cancer. However, resection of sessile, broad based pedunculated and flat lesions carries a high risk of perforation. Endoscopic mucosal resection (EMR) may significantly reduce this risk. We aim to assess the safety and efficacy of EMR in our unit.

Methods: A review of prospective database over a 3 year period identified 87 patients who underwent endoscopic polypectomy for polyps in sizes from 10 to 80 mm, performed by two experienced endoscopists. A total of 33 EMRs were performed on 30 lesions in 24 of these patients.

Results: Median size of lesions was 20 mm. Most (57%) were located in the rectum and sigmoid. On endoscopic criteria these were categorised as sessile (17), pedunculated (6), and flat (7) lesions. 22 lesions were resected en-bloc while 8 were resected piecemeal due to their size and nature. Histologically these lesions were predominantly adenomatous polyps. Adenocarcinoma was found in 7 lesions. Histologically complete excision was achieved in 10 lesions. Although histological confirmation of completeness of excision was not possible in 19 lesions, repeat colonoscopy confirmed successful excision. Only one lesion was incompletely excised requiring surgical resection. Bleeding occurred during 2 EMRs but they were successfully controlled by injection of 1:10000 adrenaline locally. There was no case of bowel perforation. Further surveillance colonoscopy was performed according to BSG guidelines. None of the patients diagnosed with adenocarcinoma have shown any evidence of recurrence since their resection.

Conclusion: Within our unit EMR appeared to be safe and effective procedure in the resection of early cancers and polyps not suitable for conventional polypectomy. These data would support prompt referral of lesions fulfilling these criteria to specialist units offering this service to avoid unnecessary surgery.

204 INJECTION SOLUTIONS FOR EMR

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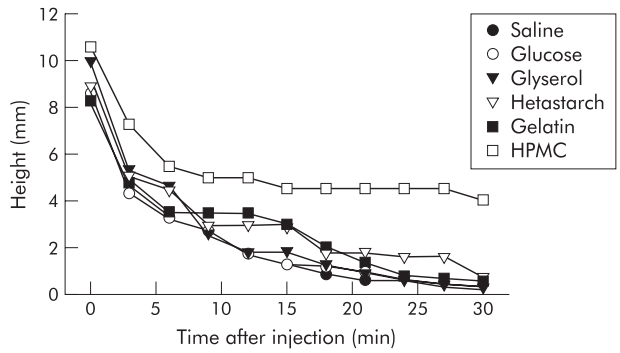
Background: Submucosal injection is essential for endoscopic mucosal resection (EMR) of flat lesions. Saline based solutions have been commonly used, though provide only short lasting submucosal cushion. The aim of this study is to compare mucosal lifting property and readiness for injection of currently available solutions, to establish the most clinically effective solution for EMR.

Methods: Three blebs were made by each injection of 0.9% normal saline, 50% glucose, 10% glycerol, 6% hetastarch, 4% gelatin, or 1% hyproxypropyl methycellulose (HPMC) with a 23G needle in the submucosal layer of freshly resected human colonic specimens. Height of each submucosal cushion was measured every 3 min after injection. Difficulty in injection was evaluated by recording the time and efforts required to empty syringes including 1.5 ml solutions via the endoscopic injection needle.

Results: Change in the height of submucosal cushion was shown below.

Syringe emptying time was 4.0, 5.8, 4.0, 3.7, 4.7, and 26.2 sec for saline, glucose, glycerol, hetastarch, gelatine, and HMPC, respectively. The former 5 solutions were smoothly flushed, while HMPC required extremely hard effort.

Conclusion: 1% HPMC, a comparatively economical material, provided the most long lasting effect; however manual injection of this solution was difficult because of its viscous nature. A supporting system for injection such as a balloon inflation syringe would be helpful for the clinical application.



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205 ENDOSCOPIC MUCOSAL RESECTION OF LARGE COLORECTAL NEOPLASMS

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Introduction and Aims: Endoscopic mucosal resection (EMR) is the treatment of choice for many large, sessile colorectal adenomas. The aim of this study was to assess the feasibility and safety of the EMR for large colonic lesions.

Methods: Retrospective analysis was performed for 107 patients who underwent EMR for large (>2 cm) colorectal tumours over a 6 year period by an experienced colonoscopist (BPS). Submucosal lifting was performed with either saline (31), saline-adrenaline (43), or saline/aderenaline/methyleneblue (33) prior to snare resection. Argon plasma coagulation was applied to resected margins as required. A clinical clearance was defined as no recurrence at the next follow up colonoscopy.

Results: Median lesion size was 3 cm (2–3 cm (44), 3–4 cm (29), >4 cm (34)). The lesions were removed in one piece in 6.8% (2–3 cm) and 0% (>3 cm). Accumulate clinical clearance rate was 55% at 1st, 79% at 2nd, 86% at 3rd, 88% at 4th, and 89% at 5th attempt. Four patients had recurrence after previous recurrence negative colonoscopy during follow up. Histologically, 78% of resected lesions were proven to be mild/moderate adenomas 13% in severely dysplastic, and 4% in adenocarcinomas with 2 cases of metaplastic polyps. Clearance failure was due to advanced histology, that is, cancer in 3 cases (with ''non-lifting sign''), repeated recurrence in UC patient (1), massive recurrence (1), or recurrence on the anal canal (1). All these patients were referred for a surgical operation. Minor bleeding was the only immediate complication in 4 cases, which are all in adrenaline/saline solution group but in 3 cases whose lesions are over 4 cm. These were treated endoscopically.

Conclusions: By applying this technique, clinical clearance was achieved in 89% of all patients. Although piecemeal resection is associated with higher recurrence rates, almost all recurrence was treated successfully at follow up endoscopy. Several repeat endoscopies may be required for some cases and long term follow up may be required to ensure complete clearance is achieved. EMR continues to be the treatment of choice for the removal of large sessile adenomas.

206 PROSPECTIVE AUDIT OF THE INTRODUCTION OF EUS-FNA TO A REGIONAL PANCREATICO-BILIARY CANCER CENTRE

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Introduction: Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) of the pancreas, adds the potential for tissue diagnosis to the staging information already provided by EUS. The sensitivity of EUS-FNA in the detection of pancreatic malignancy varies between 64-96% with a complication rate of about 2%. These reports are largely from highly experienced operators with the availability of ''in room'' cytologists.

Aim: To audit prospectively the yield, sensitivity, specificity, complications, and clinical impact of the introduction of a EUS-FNA service in a regional pancreatic cancer centre performing in excess of 300 EUS procedures a year.

Methods: All procedures performed by KO or DR using a Pentax EG383OUT linear echoendoscope, Hitachi EUB 6500 ultrasound machine, and Wilson-Cook 22 gauge FNA needles. Procedures were performed as a day case unless the patient was already an inpatient. A cytologist was not present for any of the procedures.

Results: In the first 6 months 34 EUS-FNA procedures were performed. 24 procedures were performed in 22 individuals for suspected pancreatico-biliary tumours. The aspirate was acellular or unsatisfactory in 4 procedures (16.6%). 12 procedures yielded positive cytology: 6 pancreatic adenocarcinomas, 2 mucinous tumours, 1 metastatic hypernephroma, 1 GB cancer, 1 IPMT, and 1 neuroendocrine tumour. 8 procedures yielded benign cytology. 2 of these were subsequently found to have malignancy on alternative tissue sampling, 1 patient has been operated on and found to have benign disease. 4 patients are pending surgery and 1 patient has a preexisting diagnosis of chronic pancreatitis. There were no immediate complications. 1 patient was readmitted the following day with mild pancreatitis, overall complication rate 2.9%.

Conclusion: Results in line with those in the published literature are achievable at the start of a EUS-FNA service. The relatively high rate of unsatisfactory aspirates supports the presence of a cytologist for this procedure.

207 AUDIT OF EMERGENCY ENDOSCOPY AT A DISTRICT GENERAL HOSPITAL HOSPITAL

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Introduction: Acute gastrointestinal (GI) bleeding can be effectively treated with endoscopic therapy that requires experienced personnel. At Kent and Canterbury hospital, a DGH serving 200 000 people, there are 2 consultant gastroenterologists providing this service on an ad hoc basis, with no specialist endoscopy staff cover. We analysed the number of gastroscopies performed out of hours for gastrointestinal bleeding over a 7 month period and compared those requiring intervention (either sclerotherapy or variceal banding) within working hours.

Method: We reviewed endoscopy reports on endoscribe® for a 7 month period—February to September 2003 and examined the hospital notes.

Results: There were 208 requests for gastroscopy that stated haematemesis and/or maleena. 7 gastroscopies were performed out of hours and 14 out of 201 patients within working hours required intervention. Out of hours: there were 4 males and 3 females with a mean age 61.4 year (age range 38–80 year). One required oesophageal banding (male 58 year) and 5 sclerotherapy with 1:10 000 adrenaline. In one patient no bleeding or ulcer could not be identified. Three proceeded to laparotomy. No patients died. Normal working hours: there were 8 male and 6 female with a mean age 73 years (age range 34–90 years). 2 required oesophageal banding (male—50 years, female—34 years), both survived. 12 required sclerotherapy with 1:10 000 adrenaline. None proceeded to laparotomy. 2 died, one (male—76 years) suffered a cardiac arrest prior to laparotomy and the other (male—84 years) rebled and treatment was not considered appropriate due to comorbidity. The overall mortality was 1%.

Conclusion: The out of hours selection by the consultants on-call was good with all requiring intervention or surgery. These patients were significantly younger. The overall mortality was lower than expected. The BSG framework for provision of endoscopy in DGHs states that ad hoc arrangements are no longer acceptable and that a business proposal should be submitted by each hospital to provide an on-call rota including nursing staff. However, the number of procedures that were performed out of hours over this 7 month period clearly does not justify the funding of such a rota and thus, this service will continue to depend upon the consultants' goodwill.

1. Barrison IG, *et al. BSG working party report* 2001.

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208 BARRETT'S OESOPHAGUS: AN AUDIT OF SURVEILLANCE OVER A 15 YEAR PERIOD

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Introduction: Published reports of endoscopic surveillance of patients with Barrett's oesophagus (BO) have concentrated on the development of dysplasia and adenocarcinoma. No studies have audited what happens to patients with BO with regard to entry into or continuation with endoscopic surveillance programmes.

Methods: We have audited our surveillance programme since 1987.

Results: During the years 1987–2002, 437 patients with BO were diagnosed (368 long segment (>2 cm)); 26 had oesophageal adenocarcinoma at diagnosis; 200 (177 with intestinal metaplasia (IM) on biopsy) had at least one surveillance endoscopy, and 211 have not been re-endoscoped. Of the latter, 34 were within 2 years of diagnosis and 177 have not been re-endoscoped because of no IM (43), age (44), non-attendance (39), severe concurrent illness (23), not referred back by GP (19), and miscellaneous causes (6). The 177 patients with IM (162, long segment) who had endoscopic surveillance consisted of 96 males and 81 females (aged 62.9 years (36–96 years)) and were followed up for a total of 907 patient years (average 5.48 years) and had 504 endoscopies (average 2.8/patient). 106 patients remain under active endoscopic surveillance but 71 have dropped out because of age (27), non-attendance (21), death (9; 1 from oesophageal adenocarcinoma), and miscellaneous causes (12). Of the 177 patients with IM, 4 developed low grade dysplasia, 1 high grade dysplasia, and 4 adenocarcinoma (1 cancer in 245.5 years of follow up, incidence 0.41%). 144/177 have been maintained on PPI treatment.

Conclusions: A majority of patients with BO either do not enter or do not continue in an endoscopic surveillance programme. This needs to be acknowledged when the workload and cost of BO surveillance programmes are considered.

209 ENDOSCOPIC ABLATION OF BARRETT'S OESOPHAGUS: A RANDOMISED TRIAL OF PHOTODYNAMIC THERAPY (PDT) VERSUS ARGON PLASMA COAGULATION (APC)

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Background: Barrett's oesophagus (BO) is the major risk factor for adenocarcinoma of the oesophagus, which is increasing in incidence more rapidly than any other cancer in the Western world. BO confers a lifetime risk for developing adenocarcinoma of 10–15%. Both PDT using 5-aminlaevulinic acid as a photosensitiser and APC have been shown to be effective in the ablation of BO, but a comparative trial of these two modalities has not been reported.

Materials and Methods: Sixty eight patients (55 male, 14 female; median age 61 years, range 28–81 years) with biopsy proven BO (median length 4 cm, range 2–15 cm) were randomised to receive either photodynamic therapy (PDT) (n = 34) or argon plasma coagulation (APC) (n = 34). PDT was performed using 5-aminolaevulinic acid (ALA) at a dose of 30 mg/kg, followed by laser endoscopy under sedation 4–6 hours later using a windowed balloon applicator and red (635 nm) light at 68 mW/cm^2, with a total fluence of 85 J/cm^2. APC was administered at a gas flow of 2 l/min and power setting of 65 W. Multiple treatment sessions (up to a maximum of five) were performed until macroscopic squamous re-epithelialisation was achieved. Endoscopic follow up with 4 quadrant biopsies was performed at 1, 6, 12, and 24 months.

Results: All patients in both groups showed a macroscopic reduction in the length of treated BO, with biopsy proven squamous re-epithelialisation. This was greatest in the APC group with 33 of 34 (97%) ablated (median number of treatments 3, range 1–5). In the PDT group complete ablation was achieved in 17 of 34 (50%) (median number of treatments 4, range 1–5). In the remainder, there was a reduction in the length of columnar epithelium (median reduction 50%, range 5–90%). The median follow up is 12 months (range 1–24 months) in both groups. There was one patient with recurrence of BO after 6 months in the PDT group. All patients treated with PDT suffered from transient nausea and vomiting, and there were photosensitivity reactions in 6 patients (17%). Patients treated with APC developed transient odynophagia. One patient developed an oesophageal stricture following APC, which required dilatation. There was no other treatment related morbidity.

Conclusions: PDT and APC are both effective modalities for ablating Barrett's oesophagus. PDT requires more equipment and is more costly in the short term. APC appears to be more effective than PDT for ablation of Barrett's oesophagus, but the impact of both regimes on the development of carcinoma requires larger studies with long term follow up.

210 AN EFFECTIVE SURVEILLANCE PROGRAMME FOR BARRETT'S OESOPHAGUS IN A DISTRICT GENERAL HOSPITAL

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Aim: To review the effectiveness of an endoscopic surveillance programme for patients with Barrett's oesophagus (BO).

Methods: All patients with BO over the period January 1997 to October 2002 were identified from endoscopic and histological records. Two yearly surveillance endoscopies with quadrantic biopsies at 3 cm intervals were performed in patients with classical Barrett's oesophagus (>3 cm histologically proven columnar lined oesophagus). Patients with lesser lengths of BO, significant co-morbidity or age over 75 years were excluded. Dysplasia when identified led to repeat endoscopy at 3–6 weeks if high grade (HGD) or 3–6 months if low grade.

Results: 121 patients (24%) entered the surveillance programme of 505 patients identified with BO over the 70 month period studied. 205 endoscopies were performed for surveillance with a mean period of surveillance of 3.5 years. 65% entered remained in the surveillance programme as of October 2002. The mean age at diagnosis was 60.2 years with male predominance (69.5%) and a mean length of Barrett's mucosa at the initial endoscopy of 7.5 cm. Five cases of HGD and 2 cases of adenocarcinoma were detected during surveillance. One patient with HGD refused surgery and died 2 years later of carcinoma oesophagus. The repeat biopsies in 3 of the 4 remaining patients who initially had HGD showed frank adenocarcinoma. Preoperative CT scans were clear of local or metastatic spread. These 6 patients underwent radical oesophagectomy and 5 of the 6 resected specimens showed early (T1, N0) adenocarcinoma with the other showing HGD. All patients remain well and tumour free after 24 months (mean, range 13 to 52 months). No interval oesophageal cancers occurred.

Conclusion: Our surveillance programme for Barrett's oesophagus seems very efficient in detecting early carcinoma and seems to offer successful treatment without an excessive endoscopic workload. It stands in stark contrast to MacDonald's study.[1] This might be explained by differences in inclusion criteria for surveillance.

1. MacDonald CE, Wicks AC, Playford RJ. *BMJ* 2000;**321**:1252–5.

211 METAPLASIA-DYSPLASIA-ADENOCARCINOMA SEQUENCE IN COLUMNAR LINED OESOPHAGUS (CLO) IN A LARGE UK SERIES

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Introduction: Columnar lined oesophagus (CLO) has been recognised as the main predictive indicator of oesophageal adenocarcinoma (AC). However, controversy exists as to the level of risk of malignant transformation from different histological features and this has not been studied previously in a large UK series.

Patients and Methods: Medical records of 473 patients with at least 2 biopsies from their CLO were examined and data on diagnostic CLO length and histological features (subdivided into CLO only (CLO-), CLO with intestinal features (CLOim), low grade dysplasia (LGD), high grade dysplasia (HGD) and AC). Total 1691 histology reports, average follow up 4.8 (SD 3.6) years. Average age at diagnosis 59.7 years (no significant difference between histological groups).

Results: 23 patients in total developed AC during the follow up period (annual incidence 1.01%). Risk of AC development increased with more dysplastic diagnostic histology. 19 patients who developed AC had diagnostic length available, 6 (31.6%) had short (<3 cm) segment CLO (1 of whom did not have intestinal metaplasia).

Conclusions: Data from this cohort demonstrate an escalating risk of AC with histology, particularly in the presence of dysplasia. The AC incidence in LGD is 5.3% and in HGD 50%. Overall the incidence of AC is 1.01% p.a. However, the absence of histologically documented intestinal metaplasia and the presence of short segment CLO are both associated with adenocarcinoma development.

Abstract 211

Diagnostic histology	N (% of cohort)	N (%) developing AC	N with intermediate histology
CLO-	137 (30.0%)	5 (3.6%)	2
CLOim	256 (54.1%)	12 (4.7%)	3
LGD	76 (16.1%)	4 (5.3%)	1
HGD	4 (0.8%)	2 (50.0%)	–

212 TWENTY YEAR FOLLOW UP OF PATIENTS WITH REFLUX OESOPHAGITIS: LONG TERM CONSEQUENCES AND COMPLICATIONS

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Introduction: Reflux oesophagitis is the most common abnormal finding at OGD yet the long term outcome of the condition is unknown. This study assessed the level of reflux symptoms, drug consumption and complications in patients 20 years after diagnosis of oesophagitis.

Methods: 152 patients with typical reflux symptoms and a first time diagnosis by endoscopy of grade 1 to 3 oesophagitis (modified Savary-Miller) between 1981 and 1984 at one centre were followed up using a postal questionnaire and telephone interview. The same cohort had previously been followed up 10 years after initial diagnosis (*Gut* 1996;**38**:481–6).

Results: Thirty five (23%) of the 152 patients were deceased, 6 could not be traced, 30 failed to respond, and 81 replied (mean age 63 years, range 39–88 years) with mean follow up time of 20.5 years (range 230–268 months). Fifty nine patients (73%) still had reflux symptoms at least daily (9) or weekly (19) or required daily acid suppression therapy (31). Forty six (57%) patients remained on daily acid suppression with either a proton pump inhibitor (36) or H2RA (10). Three patients (2%) developed a benign oesophageal stricture during follow up and 2 (2%) developed Barrett's oesophagus. There were no deaths due to oesophageal cancer but two deaths due to throat cancer.

Conclusion: Nearly three quarters of patients previously diagnosed as having reflux oesophagitis still had significant morbidity related to gastro-oesophageal reflux disease 20 years after diagnosis.

213 RISE IN OESOPHAGEAL ADENOCARCINOMA IS ACCOMPANIED BY SIMILAR RISE IN ORAL CANCER: EVIDENCE FOR ENVIRONMENTAL CARCINOGEN

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Introduction: Oesophageal and gastric cardia adenocarcinoma have increased in incidence two- to threefold in the Western world over the past 20 years. Scotland has the highest recorded incidence of such cancers. The high luminal concentrations of nitrite present in the oesophagus may contribute to oesophageal adenocarcinoma as it can be converted to carcinogenic *N*-nitroso compounds by bacteria or acid. The oral cavity has the same nitrite concentration as the oesophagus both derived from the enterosalivary recirculation of dietary nitrate.

Aims: To compare the changes in incidence of epithelial cancers in the anatomical regions exposed to high luminal nitrite concentrations with those not exposed to nitrite. The data on cancer incidence were obtained from the Scottish Cancer Registry and are presented as world age standardised rates.

Results: Change in cancer incidence in males between 1975–99 (see table).

Conclusion: In Scotland, the rise in oesophageal adenocarcinoma has been accompanied by a similar rise in oral carcinoma and also significant increase in oesophageal squamous carcinoma. This suggests exposure to a luminal carcinogen. The epithelia showing an increase in cancer all have high luminal nitrite concentration which may be the pre-carcinogen. The rise in these cancers is occurring 20 years after the marked rise in nitrogenous fertiliser usage which is the source of dietary nitrate.

Abstract 213

High luminal nitrite				No/low luminal nitrite		
	Oesophagus					
Oral cavity	Adeno Ca	Squamo Ca	Cardia	Resp tract	Salivary glands	Pancreas
+151%	+195%	+60%	+230%	−31%	−20%	−12%

The overall incidence of cancer (all sites combined) has not changed over this time period.

214 THE OESOPHAGEAL LUMEN HAS THE CHEMICAL CONDITIONS FOR GENERATING CARCINOGENIC *N*-NITROSO COMPOUNDS

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Background: Bacteria in the oral cavity reduce 25% of the nitrate, absorbed from the diet and secreted into the mouth by the salivary glands to nitrite. Nitrite can be converted to carcinogenic *N*-nitroso compounds (NOC) (1) by bacteria at neutral pH and (2) non-bacterially at acidic pH catalysed by thiocyanate (SCN) which is also secreted in saliva. The concentrations of the chemicals relevant to NOC generation have been studied previously in the mouth and the stomach but not in the nasal cavity, pharynx and different regions of the oesophagus.

Aim: To study the concentrations of the chemicals relevant to *N*-nitrosation in the nasal cavity, pharynx, proximal and distal oesophagus under fasting conditions and following ingestion of nitrate.

Methods: Seven healthy volunteers were studied. A microdialysis probe was positioned at each of the four anatomical locations and samples collected for 40 mins under fasting conditions and 30 mins following intragastric instillation of 2 mmol nitrate.

Results: See table.

Conclusion: The oesophageal lumen contains high concentrations of nitrite and thiocyanate and thus provides the conditions for generation of *N*-nitroso compounds by bacteria at neutral pH or by acidification during reflux episodes. These compounds are likely to contribute to the development of both oesophageal squamous and adenocarcinoma.

215 RESULTS FROM A FIVE YEAR COHORT OF PATIENTS UNDERGOING SURVEILLANCE FOR BARRETT'S OESOPHAGUS

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Background: Barrett's oesophagus (BO) is recognised as a premalignant condition for oesophageal adenocarcinoma. The effectiveness of endoscopic surveillance programmes in detecting early stage cancers and in improving outcomes is controversial.

Aims: To measure the incidence and outcome of adenocarcinoma in a BO surveillance programme over a five year period and to evaluate the outcome of surveillance detected cancers.

Subjects: All patients with Barrett's oesophagus attending the Royal Bournemouth Hospital endoscopy unit between 1998 and 2002 were identified.

Methods: Patients with oesophageal columnar and intestinal metaplasia were identified using the pathology computer database.

Results: We identified 474 patients with known BO in a surveillance programme with a mean age of 65 years. 54 BO associated adenocarcinomas were detected during the study period. Eight (15%) were diagnosed as a result of surveillance endoscopy. 46 (85%) were diagnosed de novo at index endoscopy. The eight patients with adenocarcinoma in the surveillance programme were all early stage (<T2 N0). Six underwent oesephago-gastrectomy. Two had endoscopic mucosal resection. 7/8 patients have survived to date (range 17–53 months, median 42 months). One patient died at 41 months. No interval cancers occurred. The oesophageal malignancy rate was 0.58% a year for patients in the surveillance programme. Cancer incidence per patient year of follow up was 1 in 171. De novo BO associated cancers were more advanced. Of these 15 patients underwent oesophago-gastrectomy. 9/15 patients have survived to date. 31 patients were suitable only for palliative therapy. Of these 24/31 patients have died.

Conclusions: Oesophageal cancers detected during surveillance endoscopies were generally diagnosed at an earlier stage than de novo BO associated cancers. Surveillance cancers were resectable and had a better outcome than de novo cancers. Our study supports endoscopic surveillance of selected patients with Barrett's oesophagus.

Abstract 214

	Nitrate		Nitrite		SCN	
	Fasting	Post nitrate	Fasting	Post nitrate	Fasting	Post nitrate
Nasal cavity	13 (7)	46 (9)	0 (0.1)	0 (0)	89 (15)	82 (14)
Pharynx	54 (7)	307 (70)	11 (6)	141 (61)	448 (154)	481 (147)
Mid oesoph.	97 (10)	817 (225)	31 (9)	278 (94)	758 (225)	826 (230)
Dist. Oesoph.	90 (11)	732 (214)	31 (8)	270 (98)	728 (222)	758 (233)

All values are μmol/l presented as mean (SD).

216 THE ORACLE (OESOPHAGEAL REFLUX AND CHANGE IN LIFESTYLE EVALUATION) STUDY

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Background: Gastro-oesophageal reflux disease (GORD) has significant impact on health and quality of life. An ideal treatment for GORD should improve reflux symptoms and the health related quality of life (HRQoL). Several studies exploring the causal factors of GORD have yielded conflicting reports.

Aim: To study in depth the effect of a controlled and structured dietary intervention and generic lifestyle advice on the symptoms of GORD and on the health related quality of life (HRQoL).

Methodology: All patients with non-erosive (less than grade 2 Savary-Miller classification) oesophagitis and ongoing symptoms of GORD were matched against the inclusion and exclusion criteria. Suitable patients on consenting were randomised. The patients were followed up at 3 and 6 months from baseline assessment.

Material used: The GORD questionnaire comprising of both generic and GORD targeted domains is being used. The principal outcome measure used is GORD symptom frequency (GSF), symptom bothersomeness (GSB), eating related symptom frequency and bothersomeness (ESF and ESB respectively), sleep related problems (PSL), and work disability (WD).

Results: Total number of patients was 117 with 57.26% being female. The mean baseline GSF and GSB scores (on a scale of 100) were 45.15 and 57.71 respectively. 60 patients have completed the third month follow up and the mean GSF and GSB were 56.42 and 67.39 respectively showing an increase in the scores of 11.27 and 9.68 respectively. The sixth month follow up is yet to begin.

Conclusion: (1) The rise of the scores by more than 9, indicates a positive response at the third month stage. (2) The achievement of the projected rise in the sixth month follow up GSF and GSB scores, by the third month itself indicates the interim success of the study. (3) The sixth month data will indicate the sustainability of the improved scores.

217 HOW ACCURATE IS THE CLINICAL HISTORY IN DYSPHAGIA?

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Introduction: Schatzki declared that a careful history should provide the diagnosis of dysphagia in 80% of cases.[1] We set out to ascertain whether this statement is still valid today, in the setting of a district general hospital.

Methods: We prospectively looked at all referrals for dysphagia from May 2002 to October 2003. Patients were excluded if they had either a previous history of dysphagia or prior investigation. The history was obtained with particular reference to the site of dysphagia, duration and constancy, progression, weight loss, reflux symptoms, and if dysphagia was to solids or liquids. A clinical diagnosis was made and investigations were carried out to confirm or refute this.

Results: 92 patients were assessed. F 60% M 40%; age 21–94, mean 62 years. Duration of symptoms varied from 7 days to 10 years with a mode of 4 weeks. Symptoms were constant in 58% and intermittent in 42%. Symptoms were progressive in 33 patients of which 11 had neoplasia (33%). Weight loss occurred in 26 and of those, 10 were found to have neoplasia (28%). The combination of weight loss and progressive symptoms demonstrates a higher rate of neoplasia than either symptom alone (48%). Dysphagia to liquids was due to dysmotility in 8 of 13 patients (62%). If patients described reflux this was the final diagnosis in 78%. Clinical diagnostic accuracy was achieved in 82%.

Conclusions: In our experience the clinical history remains highly accurate at predicting the diagnosis of dysphagia. Importantly a combination of weight loss and progressive symptoms shows a higher rate of neoplasia than either symptom alone. Dysphagia to liquids makes a diagnosis of dysmotility likely while reflux symptoms strongly correlate with acid related disorders.

1. Schatzki. *Am J Gastroenterol* 1959;**31**:117.

218 POSTPRANDIAL ACID POCKET AT THE GASTRO-OESOPHAGEAL JUNCTION—EFFECT OF MEAL FAT CONTENT AND POSTURE

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Background: We have previously shown that after a meal there exists a pocket of unbuffered highly acidic gastric juice at the gastro-oesophageal junction. In addition we observed that this post prandial acid pocket extended into the distal oesophagus.

Aims: To examine the effect of meal fat content and posture on the acid pocket.

Methods: Ten healthy subjects were studied using a dual channel pH electrode pull through technique. The pH electrodes were withdrawn by 1 cm increments every minute from the distal stomach into the oesophagus. The mean pH at each electrode position and the location of the oesophageal pH step up were assessed. The step up to oesophageal pH was defined by a pH>5. Each subject was studied fasting and then post prandial upright and post prandial supine after both high and low fat meals. We have previously shown that the pH step up when fasted corresponds to the squamo-columnar junction.

Results: The pull through studies revealed a post-prandial acid pocket at the GO junction in all 10 subjects. After the high fat meal the mean pH step up moved proximally from its fasting location of 43.9 cm distal to the nostril to 42.5 cm when upright ($p<0.001$) and 43 cm when supine ($p<0.01$). After the low fat meal the mean pH step up was at 43.5 cm when upright and 43.2 cm when supine which was similar to its location when fasting (43.9 cm).

Conclusions: After the high fat meal there is proximal migration of the acid pocket resulting in a more proximal pH step up point. This is particularly seen in the upright position and was not apparent after the low fat meal. The ability of fat to open the distal part of the GO sphincter is likely to contribute to acid damage of the most distal oesophageal squamous mucosa.

219 THE MAJORITY OF ADULT PATIENTS WITH ACHALASIA ARE TREATED FOR GASTRO-OESOPHAGEAL REFLUX DISEASE IN PRIMARY CARE—A FIVE YEAR STUDY

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Introduction: It is recognised that patients with achalasia are symptomatic for long periods prior to diagnosis. The average length of time from onset of symptoms to diagnosis is between two and seven years. This may be due to presenting symptoms mimicking other causes. We reviewed our own five year experience in a large district general hospital in the north of England to see how long patients had been symptomatic prior to diagnosis, the nature of their symptoms, and treatment.

Methods: A word search for achalasia was performed on all letters resulting from attendances at gastrointestinal clinics and endoscopy sessions over a five year period. The resulting patient notes were reviewed and those patients who had confirmed achalasia by both barium studies and manometry were selected (11 had barium studies alone).

Results: Of 161 patients identified, 43 were proven to have achalasia. The average length of symptoms prior to presentation to secondary care was 44.5 months. Dysphagia was the sole symptom in only 11.6% patients whereas it was associated with other symptoms in a further 72%. Weight loss and regurgitation were the next commonest symptoms. Only in 6.9% of patients was the diagnosis suspected in primary care and the majority of patients (55.8%) were treated for gastro-oeophageal reflux disease (GORD). In secondary care the diagnosis was suspected in 53.4% of patients after initial consultation.

Conclusion: This study shows that the majority of patients are symptomatic for a long time prior to diagnosis. Achalasia is rarely suspected in primary care, most patients are thought to be suffering from GORD. As achalasia is uncommon such attribution of symptoms is not unexpected. However dysphagia in the presence of regurgitation and or failure to respond to acid suppression should alert the general practitioner to the possibility of this condition.

220 REGURGITATION IN ACHALASIA OF THE OESOPHAGUS RESULTS IN DENTAL EROSION

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Introduction: Gastric acid regurgitation in patients with gastro-oesophageal reflux (GOR) is associated with dental erosion. Dental enamel/dentine demineralisation occurs at pH <5.5. In achalasia patients, lactic acid with a minimum pH of 3.5 in the oesophagus results from fermentation of retained food. We therefore hypothesised that regurgitation in achalasia patients will produce dental erosion.

Method: 15 untreated achalasia patients (6 males; mean age, 49 years) with symptoms of dysphagia and/or regurgitation were recruited after diagnosis by manometry. 32 controls (14 males; mean age, 43 years) with no GOR symptoms were selected for comparison. The two groups were aged matched ($p=0.3$) as tooth wear can be affected by age. All subjects were interviewed and dietary factors as cause of dental erosion was excluded. Total and palatal tooth wear were assessed according to the modified version of Smith and Knight tooth wear index with scores from 0–5. Score 0 translates into no wear with score 4 involving pulpal exposure and loss of the coronal enamel and dentine. Scores 2 and 3 relate to dentine exposure of varying degrees. Score 5 represents a restored surface as a result of tooth wear.

Results: Medians were used for non-parametric data comparisons. In achalasia patients, the total tooth wear was significantly higher when compared to controls in score 2 and above (mean: 22.94 *v* 8.29; median: 21.43 *v* 7.76; $p<0.001$), score 3 and above (mean: 8.76 *v* 0.23; median: 0 *v* 0; $p=0.001$) and scores 4 and above (mean: 4.52 *v* 0; median: 0 *v* 0; $p<0.037$). Palatal tooth wear was also found to be significantly more prevalent in patients with achalasia compared with controls in score 2 and above (mean: 65.95 *v* 0; median: 45 *v* 0; $p<0.001$), score 3 and above (mean: 30.95 *v* 0; median: 0 *v* 0; $p=0.007$) and scores 4 and above (mean: 19.05 *v* 0; median: 0 *v* 0; $p=0.031$).

Conclusion: Achalasia patients with regurgitation have significant dental erosion. It is more likely that the tooth wear is caused by oesophageal lactic acid than gastric acid.

221 GASTRIN INDUCES CYCLOOXYGENASE (COX)-2 EXPRESSION IN BARRETT'S OESOPHAGUS

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Background and Aims: The COX-2 enzyme is induced in inflammation and cancer. Furthermore, it is expressed in Barrett's epithelium (BE) and associated adenocarcinoma (AC). However, there are no previous longitudinal studies that examined COX-2 expression in the progression of BE to cancer. Furthermore, the possible role of gastrin in inducing COX-2 has not been analysed, although most BE patients use proton pump inhibitors that may cause moderate hypergastrinemia. It is also possible that there is autocrine production of gastrin by epithelial cells. This study was designed to investigate the role of COX-2 in BE and the associated AC and its relation to gastrin.

Methods: Immunohistochemistry was utilised to examine COX-2 expression in 27 BE patients (9 progressed to AC and 18 did not) followed yearly for a mean of 4.8 years. Semi-quantitative RT-PCR was used to determine gastrin and its CCK_2 receptor mRNA levels in the following samples (n = 30): oesophageal squamous epithelium (NE), BE, AC, and duodenal biopsies (DU), and in squamous (OE21) and BE cell lines (SEG-1, BIC-1, and OE33). Western blotting was used to determine COX-2 expression in NE and BE biopsies following gastrin stimulation in organ culture and in Barrett's cell lines.

Results: There was no difference between COX-2 expression in BE regardless of whether patients progressed to AC. However, both patient groups expressed more COX-2 over time during the follow up period ($p<0.005$). All NE, BE, DU, and AC biopsies expressed endogenous gastrin mRNA. CCK-B receptor is expressed in 75% NE, 80% BE, 60% dysplastic BE, 50% AC, and 100% DU biopsies used. Gastrin (G-17) induced COX-2 expression in NE, BE, and DU explants suggesting a possible role for gastrin in COX-2 induction and BE progression. All Barrett's cell lines expressed variable amounts of gastrin and CCK-B mRNA, and gastrin induced COX-2 in SEG-1 cells.

Conclusion: COX-2 expression occurs early in BE and increases over time. Proton pump inhibitor induced and autocrine production of gastrin by epithelial cells in vivo may have a role in inducing COX-2 in BE and AC.

222 CHARACTERISATION OF A SURGICAL MODEL OF OESOPHAGEAL ADENOCARCINOMA IN THE RAT

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Aim: To establish the validity of a surgical model of oesophageal adenocarcinoma in the rat as a useful model of human disease.

Method: Prospective analysis of the morphological changes occurring in the oesophagus of male Sprague-Dawley rats after oesophagojejunostomy. Following surgery 70 rats were randomised into 7 groups of 10 animals. The groups were sacrificed at 4 weekly intervals up to 28 weeks. Terminal pH measurements were made at the level of the oesophagojejunal anastamosis, and the oesophagi examined. Morphological changes were compared to human disease. Carcinogenesis was augmented during the time course with regular intramuscular iron dextran.

Results: 68 of 70 rats completed the study. The pH of refluxate was between 7 and 9 in all animals. All animals had extensive oesophageal inflammation. The proximal extent of inflammation from the oesophagojejunal junction increased with time. Ulceration was present in 90% of rats at 4 weeks but decreased to 10% by 12 weeks. A second peak of ulceration was observed between 16 and 24 weeks and coincided with development of tumour. Barrett's oesophagus was first observed at 8 weeks at the oesophagojejunal junction. The incidence and proximal extent of Barrett's oesophagus increased with time and inversely mirrored the change in ulceration. Tumour was first observed at 16 weeks and was present in 70% of animals by 28 weeks. 72% of tumours developed within a discernable island of Barrett's oesophagus.

Conclusion: Reflux of jejunal contents into the lower oesophagus of rats induces a series of morphological changes similar to those observed in human duodenogastro-oesophageal reflux disease. Tumour initiation and progression seems to occur in the absence of an acidic stimulus.

223 VARIABLE CYCLOOXYGENASE (COX)-2 EXPRESSION IN BARRETT'S ASSOCIATED ADENOCARCINOMA: RELATIONSHIP TO TUMOUR DIFFERENTIATION

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Background and Aims: Population based studies, animal models, and cell line experiments suggest a strong association between COX-2 and human cancer. Barrett's oesophageal epithelium (BE) expresses more COX-2 compared with normal squamous epithelium (NE). However, there are conflicting data regarding COX-2 expression in oesophageal adenocarcinoma (AC). Therefore, this study was designed to examine COX-2 expression in BE and associated AC and investigate whether this is affected by the degree of differentiation.

Methods: COX-2 expression was determined in NE (n = 25), BE (n = 34), duodenal biopsies, DU (n = 15) and AC (n = 45), and in Barrett's cell lines (SEG-1, BIC-1, and OE33) using Western blotting and immunohistochemistry. Tumour differentiation was determined using standard histological criteria and villin expression. Prostaglandin-E2 (PGE2) levels were measured in organ culture supernatant using enzyme immunoassay (EIA) after 24 hours of incubation.

Results: COX-2 and PGE2 levels were increased in BE compared with NE ($p=0.0003$ and $p<0.05$ respectively). COX-2 expression was, however, variable between AC patients and was heterogeneous within the tumour of the same patient. Grading of differentiation showed 83% agreement between histological criteria and villin immunostaining. Differentiated tumours expressed more COX-2 compared with poorly differentiated tumours, although this did not reach statistical significance. This may be explained by heterogeneity within the tumour, which was demonstrated by immunostaining. The moderately differentiated SEG-1 cell line expressed very high levels of COX-2 whereas the poorly differentiated BIC-1 and OE33 cells did not express significant amounts of the enzyme, in keeping with our immunohistochemistry findings.

Conclusion: Differentiated oesophageal AC biopsies and cell lines tend to express more COX-2 than non-differentiated tumours. However, COX-2 expression is heterogeneous within tumours making immunohistochemistry more suitable than western blotting in examining COX-2 expression levels.

224 ZOOM CHROMOENDOSCOPY TO DETECT DYSPLASIA IN BARRETT'S OESOPHAGUS

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Background: Dysplasia within Barrett's epithelium (BE) is the most practical marker for potential progression to cancer. Targeted biopsy using Zoom endoscopy may provide better yield for dysplasia.

Aim: To study the utility of methylene blue chromoendoscopy (MBC) with a high resolution zoom gastroscope to detect dysplasia in BE.

Methods: Twenty-eight patients (22 male, 6 female; age 32–82, median 56 years) with BE (3–12, median 4 cm) underwent MBC with a high resolution zoom gastroscope. Mucosal patterns seen on zoom endoscopy were: circular, ridge villous, and irregular villous or whorl like.

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Mucosal patterns	Indefinite for dysplasia	Low grade dysplasia	High grade dysplasia
Circular	1	0	0
Ridge villous	1	3	0
Complex irregular villous	0	4	1

Results: Ten patients (36%) were diagnosed with dysplasia, p = 0.005 (95% CI 0.15 to 0.76).

All the biopsy specimens from patients with dysplasia (except one patient indefinite for dysplasia) were obtained from unstained or heterogeneously stained mucosa. Circular and villous mucosal pattern was seen in diffuse staining areas. Villous and complex irregular villous patterns were seen in heterogeneous or unstained areas.

Conclusion: MBC with a zoom gastroscope helps to target biopsies to high yield (dysplastic) areas within BE. If these preliminary results were validated, it would potentially eliminate the need for random biopsies.

225 COX-2 EXPRESSION, CELLULAR PROLIFERATION, AND APOPTOSIS IN EOSINOPHILIC OESOPHAGITIS AND GASTRO-OESOPHAGEAL REFLUX DISEASE

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Introduction: Eosinophilic oesophagitis (EO) is a condition not frequently diagnosed, with patients presenting with intermittent odynophagia, dysphagia, and bolus obstruction, without any significant endoscopic or manometric findings. Some authors still consider that it is caused by reflux disease, but we feel this condition is related to an allergic response. To test our hypothesis we examined the cellular characteristics of EO and compared them to normal mucosa and to that of reflux oesophagitis.

Methods: We used archival diagnostic oesophageal mucosal biopsies of seven patients with EO, eight with reflux oesophagitis, and thirteen with a normal histological appearance. We measured quantitatively the expression of the COX-2 enzyme, cellular proliferation, and oncogenic resistance to apoptosis, using monoclonal antibodies for the COX-2 enzyme, Ki-67 and BCL-2 respectively.

Results: Five of the seven (71%) biopsies with a diagnosis of EO showed significant expression of Ki-67, indicating cellular proliferation. This compared with four of eight (50%) in the reflux group and none in the controls. BCL-2 was not significantly expressed in any of the three patient groups. In all patients of the control group COX-2 was only expressed in the basal layer and not in the squamous epithelium. This was similar in the reflux group with two patients (25%) also showing significant staining in the surface epithelium. In contrast, the EO group did not express COX-2 in any area of the biopsy sample including the basal layer.

Conclusion: EO is a proliferative condition expressing Ki-67 in higher concentrations than in normal tissue or in reflux oesophagitis. It is also differentiated from reflux disease in the expression of COX-2, as this was markedly less in the eosinophil group when compared to the control biopsies and reflux oesophagitis. The results indicate that that EO is unlikely to be related to the mucosal injury associated with gastro-oesophageal reflux, and that an allergic response is more likely.

226 CLINICAL OUTCOME OF PATIENTS WITH LOW GRADE DYSPLASIA IN BARRETT'S OESOPHAGUS

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Introduction: Barrett's oesophagus (BO) is a premalignant condition with histopathological evidence of dysplasia being the best marker of increased cancer risk. We undertook a retrospective analysis to determine the clinical outcome of patients with low grade dysplasia (LGD).

Aims and Methods: The aim was to determine the clinical outcome of LGD in patients with BO in the context of high rates of proton pump inhibitor (PPI) use. All cases with BO from 1990 to 1998 were identified from a histopathology database. Case notes were retrieved and analysed until 31 October 2000. Mortality data were obtained from the Office of National Statistics until June 2002. A subgroup analysis of all patients with LGD was undertaken.

Results: Of the 273 patients with histology confirmed BO, there were 45 patients (16.5%) with LGD and 2 patients with high grade dysplasia (HGD) identified at some point. Mean age of diagnosis was 68 (SD 12.1) years (range 32–94). 29/45 (68.4%) were males. There were 30 cases of prevalent LGD (66.6%). Of the 15 incident cases (33.3%), the mean time to diagnosis was 30.7 months (1–92 months) from the time of diagnosis of BO. LGD showed ''regression'' in 27 cases (60%) after a mean period of 12.8 months, persisted in 2 cases, 10 (22.2%) were lost to follow up and 6 cases (13.3%) were followed up until death due to other causes soon after diagnosis or study termination. Total follow up was 1216 months (101 patient years, mean 2.89 years per patient, n = 35). In the 3 cases in which LGD reappeared on surveillance endoscopy after a mean of 22.7 (SD 13.4) months, 2 persisted while one ''regressed'' after 12 months. Of 39 patients, 20 (51.3%) were on PPIs when LGD was diagnosed and all (45/45, 100%) took PPIs after diagnosis. No cases with LGD progressed to HGD or adenocarcinoma of oesophagus. 13 patients (28.9%) died of unrelated causes. **Conclusion:** In the era of PPI therapy, about two third of cases of LGD in patients with underlying BO showed ''regression'' while none progressed to HGD or carcinoma oesophagus.

227 THE TRUE RISK OF BARRETT'S OESOPHAGUS—HAS IT BEEN UNDERESTIMATED?

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Background: Barrett's oesophagus (BO) is the major risk factor for adenocarcinoma of the oesophagus, which is increasing in incidence more rapidly than any other cancer in the Western world. The risk of developing carcinoma in BO has been expressed in a number of different ways, for example from 30–125 times increased risk, 1 in 52 to 1 in 441 patient years of follow up, 0.5–1% per year, and 10–15% lifetime risk. However, much of this is based upon historical data, and the criteria for making the diagnosis have become more stringent since many of these studies were published, although recent BSG guidelines do not require intestinal metaplasia to be present for the diagnosis.

Materials and Methods: We identified from pathology records all patients between 1980 and 1994 who had oesophageal biopsies taken endoscopically. Those reported as junctional type, gastric fundic type, and intestinal types were included. All biopsies were then reclassified by 2 pathologists who were blinded to the original report. These were subsequently reported as showing the presence or absence of columnar epithelium, glandular mucosa, and intestinal metaplasia.

Results: 950 patient episodes in 712 patients were identified. Of these, 24 did not have columnar epithelium, leaving 688 patients (396 male, 292 female) for analysis. Of this, 379 (221 male, 158 female, 55.1%) were found to have intestinal metaplasia, and the remaining 309 (175 male, 134 female, 44.9%) had glandular mucosa.

Conclusions: It has been shown that intestinal metaplasia is required for the diagnosis of BO, and that this phenotype carries malignant potential. When compared with historical data, which based the risk on a variety of phenotypes, this study suggests that a smaller subgroup of patients have ''true'' BO, and thus the risk of developing carcinoma. Based on this, the potential risk of BO could be 54–226 times increased, 1 in 29 to 1 in 243 patient years of follow up, or 18–27% lifetime risk. Surveillance of BO remains controversial, but it may be that a subgroup of patients has a higher risk of carcinoma, and it is these patients that should be offered surveillance. Larger, prospective studies with long term follow up are required to define the true risk of BO.

228 ADENOCARCINOMA OF THE GASTRO-OESOPHAGEAL JUNCTION IN ENGLAND AND WALES: INCIDENCE AND EFFECT OF ACCURACY OF CANCER REGISTRATION

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Aims and Methods: To examine trends in the proportion of incidence of unspecified anatomical subsite for cancers of the oesophagus and stomach over time. Using a database for all cancer registrations for England and Wales, 1971–1999, from the National Cancer Intelligence Unit, registrations for all subcategories of gastric and oesophageal cancer were retrieved, and incidence over time calculated using a European age Standardised Ratio model (ESR). Trends over time for the

incidences were calculated using a linear regression method of least squares.

Results: Junctional adenocarcinoma (distal third of oesophagus and gastric cardia combined) increased in males from 2.4 to 9.0 per 100 000 population ESR between 1971 and 1999. Gastric cancer incidence decreased in males from 31.1 to 18.8 per 100 000. Unspecified registrations for subsites of gastric cancer also decreased in males, from 21.4 to 9.1 per 100 000. The rates of change for all subsites and unspecified subsites of gastric cancer were −0.490 and −0.397 respectively ($p<0.001$). All subsites of oesophageal cancer increased in incidence from 7.7 to 13 per 100 000, and unspecified subsite incidence increased from 5.9 to 7 per 100 000 in males; the rates of change were +0.215 and +0.099 for all oesophagus and unspecified oesophagus respectively ($p<0.001$).

Conclusion: The proportion of gastric cancer that is unspecified for anatomical subsite has decreased slightly from 66% to 55% between 1971–99 and, by inference, the accuracy of registration of gastric cancer by anatomical subsite has marginally improved. The accuracy of reporting for oesophageal cancer in the same period also seems to have improved, from 30–41% for anatomically specified subsites. The large increase in incidence of junctional adenocarcinoma amongst males cannot, however, be wholly attributed to this improved accuracy. Thus, the rise appears genuine.

229 OESOPHAGEAL ADENOCARCINOMA: A VERY BRITISH DISEASE

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Aims: To investigate which geographical areas have the highest incidence rates of oesophageal adenocarcinoma in the world.

Methods: Incidence data for oesophageal adenocarcinoma were retrieved from the Cancer in Five Continents Volume VIII database, a database comprising incidence data for all neoplastic lesions from 252 cancer registries worldwide, compiled by the International Association of Cancer Registries (IACR). Incidence data are for the period 1993–97. Cumulative lifetime risk was calculated for each registry, which describes the percentage risk of contracting oesophageal adenocarcinoma by the age of 79.

Results: Scotland had the highest incidence rates of oesophageal adenocarcinoma worldwide. Incidence rates for males were 5.9 per 100 000 population world age standardised incidence ratio (WSR), and 1.6 per 100 000 WSR for females. England and Northern Ireland, had the next highest incidence rates for males, with rates of 4.2 per 100 000 for both countries. The cumulative risk for Scottish males was 1%, and 0.27% for females, and the risk for English males was 0.71%. When compared with other worldwide registries, it was noted that the risk for Scottish males was more than twice that of males in Holland (0.48%), France (0.4%), and the USA (0.4%). In fact, the risk was more than double than that of almost all European registries.

Conclusion: According to the IACR, Scotland, England, and Northern Ireland have the highest incidence rates for oesophageal adenocarcinoma in the world. An examination of changing social trends in these populations, such as the incidence of obesity, reflux disease, cigarette, and alcohol use, may give epidemiological clues to the aetiology of this increasingly common disease.

230 ANDROGEN RECEPTORS MAY ACT IN A PARACRINE MANNER IN ASSOCIATION WITH FIBROBLAST GROWTH FACTOR RECEPTORS TO REGULATE OESOPHAGEAL ADENOCARCINOMA GROWTH

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Background: The role of androgen receptors (AR) in tumorigenesis, including transcription of fibroblast growth factors (FGFs), is established in prostate cancer but not oesophageal adenocarcinoma, where incidence is increased in males. This study examined AR and FGF receptor (FGFR) status and serum testosterone levels in human oesophageal adenocarcinoma patients. In vivo growth of an oesophageal adenocarcinoma was assessed in mice of both sex and related to AR and FGF receptors.

Methods: AR gene expression was analysed using real time RQ-PCR, AR, and FGFR protein by immunohistochemistry and fasting serum testosterone levels by immunoassay. An oesophageal adenocarcinoma cell line was grown subcutaneously in nude mice.

Results: The AR gene was expressed in normal squamous epithelium at significantly higher levels than oesophageal adenocarcinomas ($n=21$, $p=0.002$). The AR gene was expressed in the squamous carcinoma line (OE21) but not in adenocarcinoma lines (OE33 and OE19). Median serum testosterone levels in oesophageal carcinoma patients were 18.20 nM compared with 12.53 nM in age matched controls ($p=0.01$) and in those patients undergoing a curative resection, postoperative levels were lower than preoperative ($p=0.006$). AR protein was expressed in normal oesophageal squamous epithelium and the stroma of 18/23 adenocarcinoma samples. FGFR protein was expressed in malignant epithelium of 16/16 tumour samples. OE21 showed nuclear AR staining while OE33 and OE19 were negative. OE19 xenografts grew faster in male versus female mice (tumour weight at day 21, 1.139 g and 0.279 g, respectively, $p=0.005$) and had elevated AR and FGF receptor expression.

Conclusion: AR expressed in the stroma of oesophageal adenocarcinomas may induce paracrine effects following stimulation by androgens (including tumour derived), possibly via FGFs.

231 BARRETT'S OESOPHAGUS IN YOUNG ADULTS: NO INCREASE IN THE PUTATIVE BARRETT'S PRECURSOR, ''MULTILAYERED EPITHELIUM''; RAISED LAMINA PROPRIA EOSINOPHILS IDENTIFIED

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Introduction: Barrett's oesophagus may occur in children and young adults. ''Multilayered epithelium'' (ME) has been recently described as a precursor to Barrett's oesophagus, however, it has not been studied in young adults. In addition, little attention has been paid to inflammatory cells of Barrett's mucosa in this group.

Methods: The clinical, endoscopic, and histopathologic features of patients with proven Barrett's oesophagus aged 35 years or less ($n=12$) were compared to a randomly selected sex matched control patient group with Barrett's oesophagus aged 45 years or more ($n=11$). Special attention was directed to the presence of ME, in addition to the type, amount and distribution of inflammatory cells in the Barrett's mucosa.

Results: All patients in both groups had columnar lined oesophagus with intestinal metaplasia. ME was present in one patient from each group; 8% in study group and 9% in control group. Study and control patients had an overall equal amount of acute and chronic inflammatory cells in the lamina propria. However, younger patients showed a marked increase in the number of eosinophils within the lamina propria of Barrett's mucosa compared with older patients (mean/high power field (hpf) 4.9 (SEM 1.2) *v* 8.7 (SEM 2.4)). There was no increase in intraepithelial eosinophils. No difference was noted between both groups with regard to presenting features, drug therapy, and incidence or severity of active oesophagitis within squamous epithelium.

Conclusion: In this study, ME was rarely identified in either patient groups and no difference in the prevalence of ME was identified between younger and older patients. Therefore, the role of ME as a precursor lesion must remain uncertain. Barrett's mucosa in younger patients contains markedly more eosinophils in the lamina propria than in older patients. A possible pathogenetic role for these cells cannot be excluded in young patients and deserves further investigation.

232 DEFECTIVE TGF-β SIGNALLING IN THE BARRETT'S METAPLASIA-DYSPLASI-ADENOCARCINOMA SEQUENCE

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Introduction: Transforming growth factor β (TGF-β) is a multifunctional cytokine that potently regulates epithelial cell proliferation. The signal pathway for TGF-β is a known tumour suppressive pathway, mutated in many gastrointestinal carcinomas. Given that abnormal proliferation is observed in the Barrett's metaplasia-dysplasia-carcinoma sequence, we hypothesise that disruptions in TGF-β signalling may contribute to oesophageal adenocarcinoma.

Methods: At least 3 patient samples from each of: normal squamous oesophagus, Barrett's oesophagus (BE) without dysplasia, BE associated adenocarcinoma and duodenum were maintained in organ culture and stimulated with 20 ng/ml recombinant TGF-β. TGF-β responsiveness was assessed using RT-PCR for p21and a proliferation marker MCM2. The TGF-β responsiveness of a panel of oesophageal cell lines was also assessed using the MTT proliferation assay in addition to p21 and MCM2. Smad4 deficient BIC-1 BE adenocarcinoma cells were

transfected with the pRK5-Smad4 expression vector and TGF-β responsiveness reassessed.

Results: Squamous and duodenal control samples exhibited a down regulation of MCM2 expression and an increase in p21 expression in response to TGFβ. BE and adenocarcinoma samples showed diminished responsiveness to TGFβ treatment. 3 oesophageal cell lines, HET-1A (normal squamous), OE21 (squamous carcinoma), and OE33 (BE adenocarcinoma) exhibited an induction of p21 and down regulation of MCM2 expression in response to TGFβ. The BE adenocarcinoma cell lines BIC-1, FLO-1, and TE7 were unresponsive to TGFβ. In BIC-1 a point mutation in Smad4 was identified. Following restoration of Smad4 protein expression BIC-1 cells were able to complex Smad4 with phosphorylated Smad2/3, and relocate to the nucleus and undergo inhibition of proliferation in response to TGF-β treatment.

Conclusion: Barrett's oesophagus and associated adenocarcinoma exhibit defects in TGF-β responsiveness which result in uncontrolled cell proliferation. These signalling alterations, in particular Smad4, may be of importance in Barrett's carcinogenesis.

233 RAPID AND SUSTAINED SYMPTOM RELIEF WITH ON-DEMAND RABEPRAZOLE TREATMENT IN PATIENTS WITH NON-EROSIVE REFLUX DISEASE

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Background and Aim: In previous placebo (PBO) controlled studies, daily treatment with both rabeprazole (RAB) 10 and 20 mg resulted in a rapid time to first heartburn (HB) free interval in non-erosive reflux disease (NERD) patients. Rapid symptom relief is key in on-demand maintenance regimens. This multicentre, European trial assessed the efficacy of RAB 10 mg *v* PBO in on-demand maintenance treatment.

Methods: 535 patients with endoscopy confirmed NERD and moderate to very severe HB for ⩾3 of the 7 days prior to study entry were enrolled in a 4 week, open label acute trial of RAB 10 mg once daily. Patients with complete HB resolution at the end of this phase entered a double blind, randomised, PBO controlled, 6 month maintenance trial of RAB 10 mg on demand or PBO. Patients began taking medication once daily when HB occurred and discontinued only when free of symptoms for a full 24 hours. Trial end points included time to discontinuation due to inadequate HB control or any other reason, and study medication and antacid use.

Results: 418 patients with complete HB resolution at the end of the acute phase were randomised (2:1) to receive RAB 10 mg (n = 279) or PBO (n = 139) on-demand. Of patients who discontinued the trial due to inadequate HB control (6%, RAB *v* 20%, PBO; $p<0.00001$), 57% in the PBO group did so within 1 month *v* 31% in the RAB group ($p<0.0001$). Of patients discontinuing the trial for any reason, 50% in the PBO group *v* 16% in the RAB group did so within 1 month ($p = 0.0012$). During the on-demand phase, patients took RAB about one quarter (26%) of the time. Complete HB resolution was achieved with 1–2 consecutive days of medication intake in 30% of patients taking RAB *v* 18% of patients taking PBO ($p = 0.0106$); 59% of patients taking RAB had complete HB resolution with ⩽4 consecutive days of medication *v* 45% of patients taking PBO ($p = 0.0096$). The average weekly antacid use was significantly lower ($p<0.001$) in the RAB group (2 ± 0.2) *v* the PBO group (4 ± 0.5).

Conclusions: On-demand treatment with RAB achieved rapid and sustained symptom relief and reduced antacid use in patients with NERD. Therefore, RAB is a suitable choice for on-demand maintenance treatment in these patients. Research supported by Janssen-Cilag EMEA, division of Janssen Pharmaceutica NV, Beerse, Belgium.

234 OEOSPHAGO-GASTRECTOMY IN A HIGH VOLUME UNIT: OUTCOMES AND SERVICE IMPLICATIONS

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Introduction: Complex upper gastrointestinal surgery is increasingly being performed in only specialist units. The aim of the study was to examine both the surgical outcomes and the ability to deliver a service over a 41 month period in a high volume unit.

Methods: The case notes of all patients undergoing oesophagogastrectomy with a gastric pull up identified from a prospective consultant database were retrospectively reviewed.

Results: 187 patients (median age 63.4 years; range 29.3–82.6 years;M:F ratio 3.9:1) underwent surgery (55.7% trans-hiatal, 20.4% left thoraco-abdominal, 10.6% 2 stage, 8.0% 3 stage, 5.3% unresectable) between January 2000 and May 2003. 90% were seen within 2 weeks of referral and treatment was instituted after a median of 21 days (range 1–90 days). The main indication for surgery was invasive malignancy in 167 patients (89%) of whom 82 (49%) had received neoadjuvant treatment. The median length of hospital stay was 14 days (range 7–69 days). 28 patients (15%) were admitted to ICU with a median stay of 10 days (range 1–44 days); a total of 337 ICU bed days were consumed during this period, accounting for 0.9% of ICU bed availability. 12 patients (6.4%) were returned to theatre, most commonly for bleeding. 30 day mortality was 0.5% (1 death) and inhospital mortality was 1.1% (2 deaths). Clinical anastomotic leaks occurred in 14 patients (7.9%) and radiological leaks without any clinical compromise in a further 6 patients (3.4%). For patients with invasive malignancy, R0 resection was achieved in 72 patients (47%), R1 in 80 patients (49%; positive radial margins in 74 patients) and R2 resection in 6 patients (4%). During the same period, national waiting list targets for both hernia repair and cholecystectomy were achieved.

Conclusions: High volume specialist units can deliver both good outcomes and an efficient service without detrimental effect upon other hospital services.

235 OMISSION OF NASOGASTRIC TUBE PLACEMENT FOLLOWING UNCOMPLICATED LAPAROSCOPIC NISSEN FUNDOPLICATION REDUCES HOSPITAL STAY

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Backgound: The use of nasogastric tubes routinely in patients undergoing abdominal operations is associated with increased morbidity. Nasogastric tube placement for at least 24 hours following laparoscopic Nissen fundoplication is common practice. The aim of this study was to determine the impact of this on duration of inpatient stay.

Method: Retrospective analysis of outcomes for 116 patients, who had undergone Nissen fundoplication, was made. At the time of operation, patients were randomly assigned to the first group, where the nasogastric tube was removed intra-operatively, or the second, where it remained in situ for at least 24 hours. Respective lengths of hospital stay were recorded. Data were expressed as mean (SEM).

Results: Patients were matched for age (mean age both groups, 49.5 years), sex (M:F 2:1 both groups), weight (BMI 28 (4) with NGT placement, 30 (6) without NGT) had similar co-morbidities and operation times. Those who had early removal of nasogastric tube (n = 51) had a mean inpatient stay of 1.61 days while those who had the routine placement for 24 hours postoperatively (n = 65) had a mean stay of 2.58 days, $p<0.0001$.

Conclusion: Patients in whom nasogastric tube replacement had been omitted following uncomplicated Nissen fundoplication have a significantly reduced duration of hospital stay.

236 AN ANTI-APOPTOTIC ROLE FOR GASTRIN IN BARRETT'S OESOPHAGUS

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Background and Aims: Barrett's oesophagus (BO) is a premalignant disorder of the distal oesophagus, characterised by a metaplastic change from normal squamous to intestinal type epithelium. This study assessed gastrin and cholecystokinin-type 2 receptor (CCK-2R) levels in normal and BO biopsy samples and related these to activation of the anti-apoptotic factor, protein kinase B/Akt (PKB/Akt).

Methods: Expression of gastrin (n = 16) and CCK-2R (n = 18) in normal and BE human biopsy samples was quantified via real time (RQ) PCR. Effects of exogenous gastrin stimulation on PKB/Akt phosphorylation and IκBα degradation in two CCK-2R positive oesophageal cell lines was assessed via western blotting with gastrin gene expression determined via real time PCR. Immunostaining confirmed expression of gastrin and CCK-2R in the cell lines and of PKB/Akt in the biopsy samples.

Results: RQ-PCR showed gastrin ($p = 0.0076$) and CCK-2R ($p = 0.0068$) to be significantly upregulated in BO compared with paired normals. Exogenous amidated gastrin increased phosphorylation of PKB/Akt in OE33 cells. PKB/Akt was constitutively phosphorylated in OE19 cells, which had higher gastrin gene expression. Furthermore, phosphorylated PKB/Akt was higher in BO when compared with normal biopsies. Basal IκBα inversely correlated with PKB/Akt phosphorylation levels.

Conclusion: Exogenous gastrin via the CCK-2R up-regulates PKB/Akt phosphorylation in oesophageal cell lines. Endogenous gastrin may contribute to basal PKB/Akt phosphorylation and degradation of the downstream target IκBα. Gastrin and CCK-2R expression increase as BO develops potentially explaining the increase in activated PKB/Akt. These findings suggest a role for gastrin in progression to oesophageal adenocarcinoma through PKB/Akt activation, IκBα degradation and subsequent inhibition of apoptosis.

237 DOES THE LENGTH OF BARRETT'S OESOPHAGUS HAVE AN IMPACT ON CLINICAL PRACTICE?

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Background: There is widespread variation in clinical practice for managing Barrett's oesophagus (BO) and for surveillance in relation to the length of BO. The development of BO has been linked to gastro-oesophageal reflux and hiatus hernia (HH). We studied these findings in BO of different lengths.

Aim: To identify the frequency for the different lengths of BO, the association with RO and HH and the clinical management in relation to the length.

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BO length	Number (%)	HH %	RO %	PPI %	Surv %	Bx %	Histology Inflam	Histology IM
⩽2 cm	70 (27)	50	20	48	30	42	49	42
3–6 cm	131(50)	54	18	60	54	73	49	63
⩾7 cm	59 (23)	52	10	58	68	73	11	76

Methods: An endoscribe database search for BO over a 25 month period was undertaken. For each report the length of BO, presence of hiatus hernia (HH) and reflux oesphagitis (RO) were noted. Surveillance follow up (surv), biopsies (bx) taken and histology report for inflammation (inflam) and intestinal metaplasia (IM) were recorded.

Results: BO was observed in 260 patients. The frequency of HH, RO, and adenocarcinoma for BO ⩽2 cm is similar to longer length BO. Biopsy sampling, surveillance, and PPI use was less compared with BO ⩾3 cm. Inflammatory changes were less common in BO ⩾7 cm with more biopsies showing IM at this length. The findings are shown in the table. Six patients with adenocarcinoma were also identified; they had not had previous OGDs (BO ⩽2 cm: 1 case, BO 3–6 cm: 3 cases and BO ⩾7 cm: 2 cases).

Conclusion: BO ⩽2 cm is managed differently to ⩾3 cm BO even though the association with HH, RO and adenocarcinoma is similar to BO ⩾3 cm. Future clinical guidelines should address this discrepancy and BO endoscopy lists should focus on increasing biopsy sampling.

238 MORTALITY RISK FACTORS AND COMORBIDITY IN PATIENTS WITH BARRETT'S METAPLASIA

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Background and Aim: Barrett's metaplasia is a recognised precursor lesion for oesophageal adenocarcinoma; however it is recognised that most patients with Barrett's have other comorbidities. We aimed to assess the cause of death of patients with Barrett's in an attempt to clarify whether these patients should be screened for other diseases.

Methods: All the histologically and endoscopically proven Barrett's patients (last 5 years) were collected from the regional database and medical records of the deceased patients were retrospectively reviewed to collect information regarding comorbidity, cause of death, medication, endoscopic finds, smoking habits, and alcohol intake.

Results: 75 patients 52 male and 23 female were analysed (age range 40–100 years). Most had comorbid conditions: ischaemic heart disease 37.3%; diabetes 6.6%; CVA 22.6%; chest disease 22.6%, and other cancers (apart from oesophagus)13.3%. Most were on several drugs: aspirin/NSAID 46.6%; PPI 80%; H2 blockers 28%; calcium blokers 20%, and antacids 12%. The prevalence of smoking was 58.6%. The cause of death was as follows: sepsis 4%; GI bleed 5%; CVA 8%; other cancers 13%; oesophageal cancer 13%; cardiac disease 19%, and chest disease 30%.

Conclusion: We show that twice as many die of cardiovascular disease as die from oesophageal adenocarcinoma. This is clear justification for both cardiac protection as well as chemoprevention in this group of patients.

239 AN APPRAISAL OF THE IMPACT OF MANOMETRY ON THE MANAGEMENT OF CHILDREN WITH FEEDING DIFFICULTIES

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Background and Aims: Feeding difficulty or abnormal feeding behaviour is a common cause of failure to thrive in the neonatal period and poor weight gain in infancy and later childhood. We have assessed the impact of oesophageal manometry on the outcome of clinical management of children with feeding difficulties. Our outcome criteria were: a significant gain in BMI ($p<0.05$) following interventions initiated after manometry, and a significant improvement based on clinical evaluation.

Methods: We collated data from the clinical notes of 10 female and 26 male children with feeding problems excluding those with underlying neurodevelopmental problems. Assessment included a detailed clinical examination and collection of anthropometric data. Investigations performed were upper GI endoscopy, barium swallow with videofluoroscopy and isotope scintigraphy. The patients had oesophageal manometry only when these tests failed to reveal an underlying pathology. Mean age of patients at first presentation was 7.1 (4.4) years. Manometry was done at the age of 8.1 (4.6) years. We evaluated the patients at the age of 9 (4.3) years to assess their response to treatment. Values are mean (1 SD). In particular, we assessed the impact of oesophageal manometry on the management of the patients. Intervention measures after manometry included Botox injection of the lower oesophageal sphincter (LOS), diet modification and modification of drug treatment all based on the outcome of manometry.

Results: Our results showed that two patients had achalasia. Eighteen patients had LOS dysfunction. Of these, 11 had LOS hypertension with complete (4), partial (6), or absent (1) relaxation on swallowing. Seven had a normotensive, partially relaxing LOS. Fourteen had non-specific oesophageal dysmotility. Twenty patients have had a full clinical evaluation after manometry. Of these, 14 showed clinical improvement confirmed by a significant gain in BMI centile from the 75th to the 91st centile (paired *t* test, $p=0.001$). BMI centiles at first presentation and at manometry were not significantly different ($p>0.05$).

Conclusion: When other investigations have proven negative or equivocal, oesophageal manometry is an essential tool in the evaluation of children with feeding difficulty and failure to thrive.

240 GASTRO-OESOPHAGEAL REFLUX RELATED PAIN IN ISCHAEMIC HEART DISEASE: A CONTROLLED CLINICAL TRIAL OF LANSOPRAZOLE

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Introduction: Gastro-oesophageal reflux (GOR) and ischaemic heart disease (IHD) commonly coexist.[1] IHD patients may mistake GOR induced pain for cardiac pain.[1] Intra-oesophageal acid can trigger angina[2] or reduce exertional anginal threshold.[3] Such an effect of GOR might be likely in patients with rest or night pain. We report a double blind controlled crossover study of lasoprazole (PPI) in IHD patients.

Methods: 75 patients (60 male, mean age 65 years) with angiographically proven IHD. Inclusion criteria: exertional angina >1 episode of rest/night pain/week. Exclusions: upper GI disorders or acid suppression for dyspepsia. Patients randomised (lansoprazole 30 mg/d or placebo), crossed over after 4 weeks. Daily diary recorded chest pain. Quality of life assessed by Nottingham Health Profile Questionnaire. 65 had 24 h ECG in the final week of PPI/placebo. ST depression episodes were counted. Statistics: paired two tailed Student's *t* test.

Results: Number of pain free days increased (mean (SE) 6.7 (0.6) (PPI) *v* 5.4 (0.5) (placebo) $p<0.013$), days with nocturnal pain decreased (2.0 (0.4) (PPI) *v* 3.1 (0.5) (placebo); $p<0.018$) and days with pain at rest decreased (3.7 (0.5) (PPI) *v* 4.7 (0.6) (placebo); $p<0.035$). Exertional pain and QOL were unaffected. Number of ST segment

depression episodes were not different (PPI 1.4 (1.1); placebo 0.8 (0.5) NS).

Conclusion: PPI increases pain free days, and reduces nocturnal pain and pain at rest. As PPI did not affect ST segment depression, this effect is likely due to suppression of GOR provoked pain misinterpreted as angina rather than true ischaemia.

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241 INVOLVING PATIENTS IN THE RESEARCH AGENDA: IDENTIFYING THE RESEARCH PRIORITIES OF GORD PATIENTS

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Aims: To explore the research priorities of patients with GORD.

Rationale: It is argued that patients are the experts and have the knowledge and experience of living with disease and should be consulted about what research is being conducted. An appropriate and effective methodological tool needs to be identified to elicit patients' views and opinions about the research agenda.

Methods: In depth interviews and focus groups were conducted by a sociologist to explore GORD patients' views on research. An iterative process was used until saturation of themes was reached. Analysis was conducted using thematic framework and NVivo, the qualitative data analysis software program.

Results: A broad range of researchable topics was generated although patients were sceptical about their ability to identify useful themes and topics. Participants appreciated the opportunity to discuss their own point of view and felt they pursued their opinion to a greater depth than would otherwise be possible. Research topics suggested included: problems identifying reflux early on; effectiveness of tests and reducing discomfort; concerns about lifelong medication cost and dependency; effectiveness of treatment; causes of reflux including diet, genetic, and stress; prevention of reflux and complications; information and public awareness and education; communication with health care professionals and NHS organisation and service delivery (such as fail safe mechanisms) and provision of specialist nurse; timing and access to surgery, and prosthetic non-surgical implants.

Conclusion: These results can be used to influence and support the future research agenda. Further research could also be conducted to identify whether there is a possible mismatch between those who control the research agenda and those subjects preferred by patients.

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242 VITAMIN C INHIBITS NUCLEAR FACTOR-κB (NF-κB) ACTIVATION IN OESOPHAGEAL CELLS EXPOSED TO DEOXYCHOLIC ACID—POTENTIAL CANCER PREVENTATIVE TREATMENT IN PATIENTS WITH BARRETT'S METAPLASIA

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Introduction: Vitamin C (ascorbic acid) appears to provide protection against cancer development, although the mechanism of action is not entirely clear. Nuclear factor-κB (NF-κB) is an antiapoptotic, pro-inflammatory transcription factor that has been known to play a major role in carcinogenesis. We have shown previously that deoxycholic acid (DCA) activates NF-κB in oesophageal cells. This study aims to identify whether vitamin C has any effect on this DCA induced NF-κB activation.

Methods: OE33 cells derived from an oesophageal adenocarcinoma arising in Barrett's metaplasia were cultured with varying concentrations of vitamin C (10–100 μM). The cells were then treated with deoxycholic acid (DCA) at a physiological dose (300 μM) at neutral pH. Real time PCR and cDNA membrane arrays were used to identify and quantify NF-κB activation.

Results: Real time PCR revealed a progressive decrease in NF-κB activation with increasing concentrations of vitamin C identifying a possible mechanism by which vitamin C could prevent malignant progression.

Conclusions: NF-κB has already been linked to several cancers and we believe it may have a role in the development of oesophageal adenocarcinoma. In this study vitamin C confers a protective effect on the oesophageal cells exposed to deoxycholic acid by reducing NF-κB activation. Should all patients with GORD particularly those with Barrett's metaplasia have regular vitamin C prescribed to reduce the risk of cancer development?

243 *HELICOBACTER PYLORI* EXPRESS AN E2A HOMOLOGUE

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Previously we have shown that *Helicobacter pylori* can regulate acutely the expression of Id helix-loop-helix transcriptional regulators, at both mRNA and protein level. Specifically, Id-1 and Id-3 were down regulated two to 24 hours after exposure of gastric epithelial cells to *H pylori*. Consequently, we hypothesised that the transcriptional activity of their ubiquitously expressed partner protein, E2A, would be increased. Western blotting demonstrated two immunoreactive bands in untreated AGS gastric epithelial cells, corresponding to the molecular sizes of E47 and E12, the products of the two *E2A* splice variants. In cells exposed to *H pylori*, there was a decrease in the higher molecular weight band (E47), but a massive increase in the immunoreactivity for the smaller protein, the E12 variant. E2A mRNA expression was also analysed using RT-PCR; however, no change was seen following *H pylori* exposure. These data suggested that E47/E12 was regulated post-transcriptionally. Despite the apparent increase in E12 expression, the level of E-Box binding activity was actually suppressed in *H pylori* treated cells, as determined by electrophoretic mobility shift assay. Immunofluorescence studies identified the subcellular localisation of the E2A immunoreactivity; these demonstrated that very strong immunoreactivity was associated with the bacteria. Western blotting was used to confirm the presence, in *H pylori* cell lysates, of an E2A cross reactive protein of an identical size to the apparently strongly induced protein in the gastric epithelial cells. We propose that *H pylori* express a homologue of the basic helix-loop-helix protein E2A, and that this protein may function to regulate gene expression in infected cells.

244 SERUM FROM PATIENTS WITH ACUTE LIVER FAILURE DECREASES T CELL DIFFERENTIATION OF HUMAN STEM CELLS

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Introduction: Previous studies have shown that $CD34^+$ stem cells are mobilised in response to certain types of human liver injury, and that ability to mobilise such cells is associated with an improved clinical outcome. However the effect of human liver injury serum on isolated human stem cells in terms of necrosis and differentiation profile (hepatocytic and haematopoietic) is poorly understood.

Aim: To study the effect of acute liver failure serum on human stem cells in terms of toxicity and differentiation profile.

Methods: The $CD34^+$ *bright* stem cells ($AC133^+$) were isolated from freshly isolated human cord blood samples. Serum was collected from patients with acute liver failure, with ethical approval. Cells were cultured in 24 well plates for 2 weeks in the presence of Thrombopoietin and Flt-3 ligand. Cell necrosis was assessed flow cytometrically by Propidium Iodide exclusion. Cell differentiation was examined by rtPCR for albumin and αFP transcripts, immunofluorescence for hepatocyte nuclear transcription factors HNF4α and cEBPβ, as well as flow cytometry for a panel of haematopoietic markers.

Results: (1) Increasing concentrations of fulminant serum caused significant increases in cellular necrosis when compared with control cultures (19.6 (SD 2.21) *v* 12.5 (SD 2.62)%, $p<0.05$). (2) There was no evidence of hepatocytic differentiation seen after culture with fulminant serum. (3) There was significantly reduced ($p=0.01$) T cell differentiation of $AC133^+$ cells after culture with fulminant serum (8 (SD 2)%) compared with normal serum control cultures (18 (SD 2)%).

Conclusions: (1) Our data demonstrate that human stem cells are susceptible to increased cellular necrosis when exposed to fulminant serum. (2) Fulminant serum in in vitro culture is insufficient to induce early or late markers of hepatocytic differentiation. (3) Fulminant serum is associated with decreased T cell differentiation. This may be relevant given the reduced capacity of such patients to resist infection.

245 SECRETORY RESPONSE OF HUMAN PANETH CELLS TO BACTERIAL ANTIGENS

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Introduction and Aims: Paneth cells are specialized epithelial cells located at the base of the crypts of Leiberkühn where they release secretory granules apically into the intestinal lumen. Paneth cell granules contain several important anti-microbial peptides, including lysozyme, secretory phospholipase A2 and defensins which are critically important in host immunity, especially against bacteria in the gut. Cholinergic stimulation of Paneth cell degranulation is well known, as well as secretion of microbial defensins by murine Paneth cells in response to bacteria. In this study we aimed to use intact human crypts to measure human Paneth cell secretory responses and to quantitate the release of lysozyme.

Methods: Sections of small intestine, obtained from surgical resection specimens, were incubated in 30 mM EDTA in phosphate buffered saline (PBS) to detach the epithelium from the basement membrane. Epithelium was attached to a sterile cork board with cyanoacrylate glue (Histoacryl) and mechanically shaken, to release individual crypts. Isolated crypts were incubated in isotonic iPIPES buffer containing secretory stimuli (for example, LPS, MDP, whole bacteria) at 37°C. Crypts were deposited by centrifugation and supernatants were analysed for secreted lysozyme by western blot and ELISA.

Results and Conclusions: Lysozyme secretion was induced by stimulation of human intestinal crypts with LPS, MDP, and whole bacteria. We demonstrated that human Paneth cells secreted a maximum of 20% of their total lysozyme store. This is the first study that demonstrates secretion of antimicrobial peptides from human Paneth cells and provides a novel method of investigating intestinal defence against bacteria in humans.

246 IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES FOLLOWING BACTERIAL ENTEROTOXIN INDUCED NEURONAL GROWTH AND DIFFERNTIATION IN PC12 CELLS

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Introduction: Cholera toxin (CT), *Escherichia coli* heat labile (LT), and heat stable (ST) toxins mediate intestinal secretion in part through an enteric reflex arc; this may be via a direct effect on enteric nerves. We have shown previously that CT and LT, but not ST, induce neurite outgrowth in PC12 cells and enhance the neuronal differentiation effects of nerve growth factor (NGF).

Method: cDNA microarray technology was used to identify early gene expression in PC12 cells induced by CT, LT, and ST. The Affymetrix growth and differentiation genechip U34A was used for microarray analysis.

Results: CT and LT induced a 17.9 and 6.5 fold change, respectively in expression of NGF induced protein, an early growth response gene. NGF alone induced a 23.6 fold change in expression of this gene. CT+NGF and LT+NGF induced a 42.9 and 33.3 fold change in the expression of NGF induced protein. CT and LT induce a 17.7 and 8.5 fold change, respectively in expression of NGF induced factor A gene. NGF induced a 17.1 fold change in expression of this gene. CT+NGF and LT+NGF induced a 34.7 and 19.1 fold change in the expression of NGF induced factor A. c/EBP related transcription factor and VGF nerve growth factor inducible genes were only upregulated in the presence of CT+NGF and LT+NGF but not by enterotoxin or NGF alone: fold changes in expression were 2.1 and 1.5, respectively. No significant change in gene expression was seen with ST.

Discussion: In PC12 cells, CT and LT induce upregulation in genes involved in neuronal differentiation. A synergistic effect of CT or LT with NGF occurs in some NGF induced genes, supporting the phenotypic synergistic changes previously observed. New gene upregulation occurs when PC12 cells are exposed to CT or LT+NGF. These findings suggest that CT, LT, and NGF have separate but synergistic effects on gene expression.

247 PHARMACOLOGICAL MANIPULATION OF ANGIOTENSIN II AND TRANSFORMING GROWTH FACTOR β-1 IN MESOTHELIAL CELLS

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Background: Desmoplasia, peritoneal fibrosis and adhesion formation as seen in carcinoid tumours involve several cellular and humoral pathways. TGFβ-1 is increased at the site of adhesions and in peritoneal effluent from CAPD patients with peritoneal fibrosis. The local renin angiotensin system (RAS) has been shown to modulate TGFβ-1 expression. The aim was to establish if an active local RAS exists in the peritoneum which may regulate TGFβ-1 and hence fibrosis.

Methods: Met5A, a human mesothelial cell line, was cultured serum free and exposed to Enalaprilat and Losartan daily for three days. The effect on cell number, metabolic capacity, and TGFβ-1 and angiotensin II levels in the supernatant was assessed.

Results: Met5A cells produce TGFβ-1 and angiotensin II in vitro in serum free media. Enalaprilat inhibits Met5A cell proliferation at low (10^{-10} M, $p<0.05$) but not at high concentrations (10^{-6} M). Losartan inhibits proliferation (10^{-10} M, $p<0.05$) and more so at higher concentrations (10^{-6} M, $p<0.01$). Despite significant changes in cell number, overall metabolic activity per well remained the same in all groups. Enalaprilat cause significant dose dependant suppression of TGFβ-1 ($p<0.001$) and angiotensin II ($p<0.01$) compared with control. Losartan also reduces TGFβ-1 ($p<0.001$) in a dose-dependant manner, and paradoxically reduces angiotensin II at low doses ($p<0.005$) but not at high doses.

Conclusions: TGFβ-1 production in Met5A cells is angiotensin II dependant via the angiotensin II type 1 receptor (AT_1-R). Angiotensin II production and consequently TGFβ-1 can be suppressed using Enalaprilat, while Losartan reduces TGFβ-1 by blocking AT_1-R. This confirms the functional link between RAS and TGFβ-1 in mesothelial cells and suggests a possible role in desmoplasia, peritoneal fibrosis, and adhesion formation.

248 EXPRESSION OF NOD2 BY INTESTINAL EPITHELIAL CELLS IN AN IN VITRO M CELL MODEL

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Introduction: NOD2 is a cytosolic detector of peptidoglycans—specifically muramyl dipeptides (MDP)—and is principally expressed by cells of the myeloid lineage (monocytes, macrophages and dendritic cells). NOD2 mutations are associated with about 20% of Crohn's disease cases, suggesting that recognition of bacterial MDP via NOD2 is an important sensory pathway in gut immunity. We have investigated the possibility that NOD2 is expressed by intestinal epithelial cells expressing characteristics of endocytic M cells.

Methods: Caco-2 monolayers were co-cultured with purified T cells, B cells or monocytes for 48 hours in a transwell system before being analysed for their ability to transcytose latex beads. Epithelial cell mRNA was then analysed by RT-PCR for the presence of NOD2. Functional responses to MDP were detected by IL-8 or TNF-α ELISA.

Results: B cells and monocytes both enhanced epithelial cell transcytosis (indicative of an M cell phenotype) while T cells were less efficient. Undifferentiated Caco-2 cells expressed barely detectable transcripts for NOD2 but expression was greatly upregulated in polarised monolayers. Levels of NOD2 mRNA were also increased in response to IL-1α but not MDP itself. Epithelial cell monolayers expressing an M cell phenotype upregulated NOD2 expression compared to monolayers cultured alone. Although they expressed NOD2, co-cultured monolayers failed to respond to MDP (as assayed by IL-8 and TNF-α ELISA). When an inverted transwell system was used (allowing immune cells to migrate into the monolayer), an IL-8 response was detected. However this appeared to originate from the immune cells themselves rather the intestinal epithelial cells.

Conclusions: The Caco-2 intestinal epithelial cell line, when grown as a monolayer, expresses NOD2 and expression is enhanced when the monolayer takes on M cell characteristics following co-culture with immune cells. However, the epithelial cells remain unresponsive to MDP and a functional response requires the presence of immune cells within the monolayer.

249 EXPRESSION OF TOLL-LIKE RECEPTORS BY INTESTINAL EPITHELIAL CELLS IN AN IN VITRO M CELL MODEL

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Introduction: A number of groups have reported the differentiation of intestinal epithelial cell lines to cells with M cell characteristics

(enhanced transcytosis, altered morphology etc.) following co-culture with immune cell subsets. M cells are the main route by which gut antigens access the mucosal immune system and are thus ideally situated to detect pathogenic microorganisms. To investigate this possibilty, we have analysed Caco-2 monolayers for their expression of Toll-like receptor (TLR) mRNA transcripts following conditioning by immune cell subsets.

Methods: Caco-2 monolayers were co-cultured with CD19+ B cells or CD14+ monocytes for 48 hours in a transwell system before being analysed for their ability to transcytose latex beads. Epithelial cell mRNA was analysed by RT-PCR.

Results: Both B cells and monocytes enhanced epithelial latex bead transcytosis—indicative of an M cell phenotype. Undifferentiated Caco-2 cells expressed low levels of TLRs 1, 3, 5, 6, 7, 8, 9, and 10 (no TLR 2 and 4). However, polarised Caco-2 monolayers expressed enhanced levels of these TLRs as well as low levels of TLR4. The most abundant transcripts in the majority of samples were TLRs 1, 3, 5, and 6. Following co-culture with B cells or monocytes, the pattern of TLR expression was essentially unchanged, with most TLRs appearing to be slightly down regulated. Although the pattern of TLR expression by the conditioned epithelial cells was unchanged, the expression of a putative TLR regulator, Tollip, was particularly high in all Caco-2 samples and appeared to be upregulated following co-culture with monocytes.

Conclusions: Caco-2 intestinal epithelial cells, co-cultured with immune cells, display an M cell phenotype but express a similar TLR pattern to that of unconditioned Caco-2 cells. This suggests that M cells have the same pathogen sensing capabilities as absorptive enterocytes and that signalling via these receptors might be closely regulated by molecules such as Tollip.

250 EFFECTS OF GLUCOCORTICOIDS ON EXPRESSION OF P-GLYCOPROTEIN AND GLUCOCORTICOID RECEPTOR IN THE INTESTINAL EPITHELIUM

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Background: Glucocorticoids are the primary drug treatment in inflammatory bowel disease. However, at least 20% of patients are steroid resistant. P-glycoprotein encoded by the multidrug resistance gene 1a and 1b (mdr1a, mdr1b) in rodents and MDR1 in humans is expressed on the surface of the intestinal epithelium and is known to actively exclude dexamethasone (DEX) and other synthetic steroids from cells. Expression of the glucocorticoid receptor (GR) also governs the effectiveness of steroids. Both increased expression of P-glycoprotein and changes in glucocorticoid receptor has been implicated in steroid insensitivity. The aim of this study was to investigate the effects of DEX in vitro on P-glycoprotein and GR expression in rat intestinal epithelial cells.

Methods: Non-transformed rat jejunum epithelial cells (IEC-6) were cultured in the presence and absence of DEX in a time and dose dependent manner. GR and P-glycoprotein protein levels were measured by western blot. Results are the mean of three experiments.

Results: Western blots revealed a time dependent (2, 4, 8, 24 hours) decrease in GR levels 51%, 68%, 75%, 76% respectively by DEX (1 μM) ($p<0.01$, $p<0.001$, $p<0.005$). A dose dependent reduction in GR with decreasing dexamethasone concentrations (10^{-5} M, 10^{-6} M, 10^{-7} M) over 24 hours was noted. Cells incubated with DEX for 2–8 hours doubled P-glycoprotein levels, and by 24 hours, expression had increased fivefold ($p<0.0001$). Preliminary dose response experiments have suggested this increase in expression is inversely proportional to the concentration of DEX (10^{-5} M–10^{-8} M).

Conclusions: This study illustrates DEX regulates both P-glycoprotein and GR expression in IEC-6 cells in a time and dose dependent manner. Indeed we find similar DEX regulation of GR and mdr1a in rat colon in vivo. A reduction in GR and increase in P-glycoprotein expression would give a possible explanation behind steroid insensitivity.

251 LYSOZYME AND SECRETORY PHOSPHOLIPASE A2 EXPRESSION IN NECROTIZING ENTEROCOLITIS

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Introduction: Necrotising enterocolitis (NEC) is a severe inflammatory gastrointestinal disorder predominantly affecting neonates. A leading theory postulates that NEC develops when aberrant colonisation by enteric bacteria triggers an intestinal inflammatory response. Paneth cells secrete an array of antimicrobial peptides, such as the α-defensins, secretory phospholipase A2 type IIA ($sPLA_2$-IIA), and lysozyme in response to bacteria and bacterial products. Dysregulated antimicrobial secretion may alter the composition of the intestinal flora and favour the growth of pathogenic bacteria, and a recent study suggested that lysozyme protein expression was absent in Paneth cells. To confirm these observations and to analyse $sPLA_2$-IIA expression, we compared expression of the lysozyme and $sPLA_2$-IIA gene products in NEC, control neonates, and adults.

Methods: We performed in situ hybridisation and immunohistochemistry, using digoxigenin-labelled sense and antisense riboprobes and polyclonal rabbit anti-human antibodies, on paraffin embedded intestinal tissue from 14 neonates with NEC, 7 control neonates with intestinal atresia, and 5 control adult subjects. Interleukin 8 (IL-8) mRNA expression was measured by quantitative real time PCR in cultured cells.

Results: Paneth cells constitutively and strongly expressed lysozyme and $sPLA_2$-IIA RNA and protein in all adult sections. Positive lysozyme RNA staining (but of a fainter intensity) was seen in 50% of NEC cases and not in any control neonatal sections. Lysozyme protein was expressed in Paneth cells in control neonatal and adult sections, as well as in NEC sections where expression was also noted in infiltrating tissue leukocytes. $sPLA_2$-IIA protein was expressed in most neonatal and NEC sections although RNA expression was not detected in 2 of 14 NEC sections and 5 of 7 control sections. Intestinal epithelial cells that expressed lysozyme and $sPLA_2$-IIA constitutively did not regulate their synthesis of these products after exposure to bacterial agents, although they did regulate IL-8 mRNA expression.

Conclusion: Neonates express lower levels of lysozyme and $sPLA_2$-IIA than adults. Nonetheless, when compared with controls, increased expression of these antimicrobial enzymes is seen in NEC and is consistent with increased expression of α-defensins described in this disease, which probably occurs in response to enteric infection. Lysozyme and $sPLA_2$-IIA should be regarded as constitutive markers of Paneth cell differentiation, in contrast to inflammatory cytokines such as interleukin 8, which are induced on microbial stimulation.

252 DNA DERIVED FROM PROBIOTIC BACTERIA MODULATES HUMAN DENDRITIC CELL PHENOTYPE AND FUNCTION

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Introduction: Unmethylated CpG motifs, predominantly present in bacterial DNA, can be immunostimulatory via toll-like receptor (TLR)-9. Commensal bacteria play a role in maintaining immune homeostasis in the gut. Dendritic cells (DC) are modulated by microbial products, including DNA, to shape a developing T cell response. Therefore, we determined the effects of DNA derived from probiotic bifidobacteria, lactobacilli, and *Streptococcus thermophilus* on DC.

Methods: DC in whole blood or enriched on a metrizamide gradient were cultured with DNA derived from probiotic bacteria in the presence or absence of TLR9. DC were identified by multicolour flow cytometry as an HLA-DR+ lineage- (CD3-, CD14-, CD16-, CD19-, CD34-, CD56-) population and within this population CD11c+ (myeloid) and CD11c− (plasmacytoid) DC were assessed. Expression of activation markers (CD40 and CCR7) was analysed by flow cytometry and cytokine production (IL-10 and IFNα) was assessed.

Results: Probiotic bacterial DNA activated both myeloid and plasmacytoid DC as indicated by enhanced CD40 and CCR7 expression. DNA derived from all bacterial strains potently induced IL-10 production by an enriched DC population as assessed by ELISA. In whole blood cultures, the bacterial DNA selectively induced IL-10 in the myeloid DC population. Low levels of IFNα were transiently induced by DNA at early time points selectively in plasmacytoid DC. Blocking of TLR9 led to lower CCR7 expression on plasmacytoid DC and to decreased IL-10 production by myeloid DC.

Conclusions: Probiotic bacterial DNA was a potent IL-10 inducer but induced low levels of IFNα by DC. Given TLR9 expression by plasmacytoid DC, we suggest that bacterial DNA exerts primary and early effects on plasmacytoid DC. The effects on myeloid DC may be indirect via plasmacytoid DC or direct via as yet unknown mechanisms.

253 ANTIMICROBIAL ACTIVITY OF β DEFENSINS AGAINST *CRYPTOSPORIDIUM PARVUM*

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Introduction: The mucosal surface of the gastrointestinal tract (GI) is continuously exposed to a vast array of exogenous agents, which include dietary antigens, commensal flora, and potential pathogens. There is accumulating evidence that besides forming a physical barrier, the intestinal epithelium is also an active participant in host innate defence via the production of antimicrobial peptides, cytokines, and chemokines. Defensins are small cationic antimicrobial peptides that are increasingly being recognised as important effectors in innate immunity. We have previously shown that *Cryptosporidium parvum* (*C parvum*), a causative agent of diarrhoea in children and immunocompromised patients, differentially modulates the expression of beta defensins (β defensins) during infection. In the present study we have investigated the potential killing activity of defensins against the parasite.

Methods: *C parvum* sporozoites were exposed to recombinant human β defensin peptides (rhBD)-1 and -2 for 1 h. The viability of parasite was then determined by flow cytometry analysis and by reproduction in intestinal epithelial cell line (CMT-93).

Results: Flow cytometry analysis showed significant reduction in the viable sporozoite population in defensin treated samples. Moreover, defensin treated sporozoites added to CMT-93 cells yielded significantly less intracellular parasitic development compared to untreated sporozoites.

Conclusions: β defensins exhibit potent killing activity against *C parvum*. This confirms a critical role for defensins in innate immunity to *C parvum*.

254 RECTAL BRUSH BIOPSY—EXPLORATION OF ITS ROLE AS AN ALTERNATE SOURCE OF COLORECTAL TISSUE FOR BOWEL RESEARCH

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Background: Epigenetic changes including aberrant gene promoter methylation of colorectal cancer related genes have been documented before the development of neoplasia. These changes are currently detected in colonic mucosal biopsy samples obtained from sigmoidoscopy/colonoscopy.

Methods: A newly developed rectal brush biopsy technique was employed and DNA extraction done using stool DNA extraction kit. Extracted DNA was bisulphite modified, and gene methylation status for APC and hPP1 promoter regions was analyzed after an initial amplification step using COBRA-PCR (polymerase chain reaction) and methyl specific PCR, the PCR products run on gel electrophoresis and visualized under ultraviolet light.

Results: 49 rectal brush biopsies (14 quiescent ulcerative colitis, 27 healthy volunteers, and 8 polyp patients) were performed. DNA extraction showed a mean DNA concentration of 54.77 μg/ml and a mean total of 10.95 μg DNA. The mean A260/A280 ratio was 1.96. Three brushes lacked any detectable DNA. Methylation status for the APC and hPP1 gene promoter regions, showed a well defined appropriately sized bands on agarose gel.

Conclusions: Rectal brush biopsy is a safe alternative, relatively cheap and patient friendly procedure of obtaining cells from the colorectum. Sufficient DNA can be extracted from rectal brushes for assessment of gene methylation.

255 DETECTION OF MICROMETASTASES IN LYMPH NODES USING REVERSE TRANSCRIPTION POLYMERASE CHAIN REACTION FOR CYTOKERATIN 20: ARE WE UNDERSTAGING RECTAL CANCER?

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Introduction: Postoperative adjuvant chemotherapy in rectal cancer is determined by the presence of metastases in lymph nodes. Detection of lymph node metastases is routinely performed by light microscopy.

Conventional histology may not detect all metastases especially following neoadjuvant therapy (NAT). Cytokeratin 20 (CK20) is a cytokeratin known to be specific to colonic epithelium which may help detection of rectal cancer metastases in lymph nodes.

Aim: To detect micrometastases in lymph nodes in patients with rectal cancer, staged node negative by routine histology.

Method: Mesenteric lymph nodes from patients who have undergone neoadjuvant treatment for rectal cancer were harvested during surgery. Nodes were bisected and one half sent for haematoxylin and eosin (H&E) staining and evaluated by a single pathologist, while the other half was examined for CK20. CK20 was detected by RT-PCR.

The technique was validated by testing mesenteric lymph nodes with known metastases and nodes from patients without cancer. Twenty one lymph nodes from 6 patients (median age 46 years, range 25–55) which were negative for tumour deposits by H&E stain were assessed for micrometastases.

Results: All 21 nodes which were histologically negative for metastases were positive for micrometastases. Whereas 2 nodes with known metastases were positive for CK20, 3 nodes from non-cancer patients were negative for CK20.

Conclusions: Detection of CK20 is accurate in identification of micrometastases of rectal cancer to lymph nodes. Assessment of nodes by H&E histology risks understaging lymph node micrometastases in rectal cancer.

256 CO-ORDINATED REGULATION OF THE TUMOUR SUPPRESSOR GENE P16 BY β-CATENIN-LEF-1 AND THE ETS TRANSCRIPTION FAMILY

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Background: Cyclin dependent kinase inhibitor p16 is implicated in tumourigenesis and plays a central role in cancer of colitis. Molecular mechanisms regulating its overexpression are unknown. The p16 promoter sequence contains two DNA binding domains for the Ets family of transcription factors and for TCF-4/Lef-1. This study tests the hypothesis that the Ets transcription factor family synergises with β-catenin/Lef-1 in the regulation of p16 transcription.

Methods: Rama 37 epithelial cells were transiently co-transfected with a p16 promoter luciferase reporter construct and a combination of each of the stable mutant β-catenin, Lef-1, Ets-1 and Ets-2. p16 transcription was assessed using a luciferase assay.

Results: Overexpression of a stable mutant form of β-catenin alone weakly induced the expression of luciferase from the p16 promoter-luciferase reporter plasmid. However, cotransfection of expression vectors encoding the Ets-1 and Ets-2 transcription factors increased luciferase expression and enhanced promoter responsiveness to β-catenin and Lef-1. Other subfamily members including PEA3 could substitute for the Ets-1 and Ets-2 transcription factors. p16 promoter-luciferase activity was induced by up to 65-fold by coexpression of Ets-2, β-catenin, and Lef-1.

Conclusion: Our data show that Ets-1 and Ets-2 transcription factors synergise with β-catenin-TCF/Lef-1 leading to the upregulation of p16 transcription. These events may be implicated in tumourigenesis and provide targets for cancer prevention.

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257 RESULTS OF USE OF A ROTATION FLAP TO TREAT CHRONIC ANAL FISSURES

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Background: Treatment of anal fissures has changed dramatically in the past decade. Only a few fail to respond to medical treatment. Sphincterotomy and anal dilatation have fallen out of favour due to the risk of incontinence. Island flaps have been proposed to address this but 60–70% of the flap donor sites breakdown with complications. We proposed using a rotational flap would overcome this problem.

Methods: A local rotational flap from perianal skin was used to fill the fissure defect. 21 patients so treated have been followed up to determine fissure healing and incidence of donor site breakdown.

Results: Sixteen patients have had a complete resolution of their symptoms. Two developed a recurrent fissure. One patient had a combined fistula-fissure complex at diagnosis. This patient suffered from a breakdown of the flap and the donor site. Another patient had a haemorrhoidectomy and an advancement flap in the past. He developed problems with the donor site which was successfully managed conservatively. One patient had persistent mild pain after surgery but the cause could not be found. No patient suffered continence defects after surgery.

Conclusion: Use of a rotational flap is a simple, safe, and successful treatment for anal fissures. Donor site problems are minimized using this

approach. It should be the treatment of choice when surgery is required for anal fissures.

258 CIRCUMSTANCES IN WHICH COLONIC INVESTIGATIONS MAY FAIL TO DETECT COLORECTAL CANCER

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Background: Recent studies highlight miss rates for colonoscopy and barium enema. Special techniques such as magnifying colonoscopy are needed to detect some flat and depressed adenomas. We reviewed records on all patients presenting with colorectal cancer (CRC) over two years to identify those who had previous lower GI investigations that had not found CRC, and to examine possible causes of detection failure.

Methods: Case ascertainment was done using the clinical, endoscopy, and histopathology databases. Patients with recurrent CRC or second cancers were excluded. For the remaining 223 patients we audited all flexible sigmoidoscopy (FS), colonoscopy (COLY), barium radiology (BE), and colorectal pathology for 5 years before the diagnosis of CRC.

Results: Nine patients (4%) had undergone prior FS or COLY that had not shown CRC. Of these, three had FS only: two were later found to have proximal lesions and the other patient (aged 86 years) had rectal ulceration that two years later proved malignant. Two others had incomplete COLY 2–3 years before right sided cancer was diagnosed. In another case BE had suggested a left colon lesion in 1999. A left sided COLY was normal but in 2002 a right sided CRC was found. Two further patients were found to have CRC at polyp follow up: one was a malignant polyp removed by snare, and the other required surgery for a recurrent rectal adenoma which proved malignant. The final patient, who had been discharged from polyp surveillance 4 years previously, was the only patient in this series to develop CRC within 5 years of an unremarkable complete colonoscopy. Thirteen patients (6%) had undergone BE a median 3 (1–4) years prior to diagnosis of rectal (5 patients), sigmoid (4), descending (2), and proximal CRC (2 patients). Of these examinations six had been reported as normal, four showed diverticular disease only, two were hampered by faeces and one showed sigmoid narrowing in a patient later developing rectal cancer.

Conclusion: Lower mortality from CRC is much more likely to be achieved by more liberal use of COLY and better training in COLY than by wider use of specialist techniques such as magnifying COLY.

259 DELAYS BETWEEN DIAGNOSIS AND TREATMENT OF COLORECTAL CANCER: WILL A DEDICATED NURSE PRACTITIONER HELP?

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Introduction: The NHS Cancer plan aims to treat all cancer patients in the United Kingdom within one month of diagnosis by 2005.

Methods: A dedicated colorectal nurse practitioner was appointed in an attempt to reduce waiting times from initial diagnosis to definitive treatment (surgery or chemo/radiotherapy) in patients with colorectal cancer. Information and contact details were provided to the patient by the nurse practitioner at the time of diagnosis and the fast track staging process was initiated. This included the use of prebooked slots for cross-sectional imaging, pre-arrangement of rapid MDT discussion following staging, and same day referral to clinical oncology for patients who needed preoperative chemo/radiotherapy.

Retrospective data (n = 85) from January to June 2002 were compared with prospective data (n = 96) on fast tracked patients between November 2002 and April 2003.

Results: There was no significant difference in the time from diagnosis to treatment (median 36 *v* 42 days) between retrospective and prospective groups compared as a whole. The diagnosis to treatment time for patients referred through the two week pathway was reduced from 70 days (n = 12 pts) in the retrospective group to 45 days (n = 24 pts) in the prospective group. For the cancers diagnosed following outpatient referrals the time to treatment was increased in the prospective group (n = 22 pts) to 53 days from 42 days in the retrospective one (n = 34 pts).

Conclusions: Facilitation of investigations by a dedicated nurse practitioner improves the time to treatment in only a subgroup of patients already in the two week rule referral pathway. This may be at the expense of patients admitted outwith the two week referral who are diagnosed with colorectal cancer.

260 THE ROLE OF AN ELASTIC TISSUE STAIN IN DETECTING VENOUS INVASION IN COLORECTAL CANCER

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Background: Venous invasion by tumour is an independent prognostic indicator of both prognosis and risk of development of distant metastases in colorectal carcinoma.

Aim: To determine whether an elastica stain significantly increases the incidence of detection of vascular invasion when compared with that seen on routinely stained sections.

Methods: Two serial sections from the tumour containing blocks of 75 cases of colorectal carcinoma were stained by (1) haematoxylin and eosin (H&E) and (2) elastica, counterstained with H&E. The incidence of both intramural and extramural vascular invasion was recorded and compared to that observed at the time the tumours were originally reported.

Results: Extramural vascular invasion had been noted in 14 (19%) of the pathology reports and was observed in 18 (24%) cases when only the H&E sections were viewed in the study. It was present in 32 (43%) cases when elastica stained sections were analysed. Intramural vascular invasion was seen in 8 (11%) cases on H&E sections and 30 (40%) cases on elastica stained sections.

Conclusion: The use of elastica stained serial sections to detect vascular invasion in tumours should be recommended in guidelines for the reporting of colorectal carcinomas.

261 OVARIAN AND COLON CELL LINES CAN BE DIFFERENTIATED USING SELDI-MS PROTEIN PROFILING

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Introduction: Suface enhanced laser desorption ionisation mass spectrometry (SELDI-MS) is a technique which has been used to study proteomic patterns. The aim of this study was to determine the sensitivity of SELDI-MS in differentiating two different cell lines.

Methods: 198 protein peaks were generated from 13 cell line extracts. Ciphergen Biomarker Wizard was used to identify significant peaks and an in-house decision analysis tree was used to differentiate the two sample types.

Results: We were able to differentiate ovarian from colon cell lines using only one peptide marker with a sensitivity and specificity 84.6% and 100% for colorectal and 100% and 84.6% for ovarian.

Discussion: This initial study demonstrates the potential of SELDI-MS to differentiate two different cell lines with a high level of sensitivity and specificity. The number of cell lines used was small and needs to be increased to validating these results. If this result can be replicated in tissue samples it may be of benefit as conventional histology and immunohistochemical assays are of limited value in differentiating colorectal from ovarian metastatic deposits.

262 THE EFFECT OF ANTICOAGULANT MEDICATION ON FALSE POSITIVE RATES IN FAECAL OCCULT BLOOD TESTING

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Aims: The objective of this study was to elicit whether anticoagulant medication (aspirin, NSAIDS, and warfarin) can affect the false positive rate of faecal occult blood (FOB) testing. The data for this study were obtained from the colorectal cancer pilot screening programme conducted on Tayside in 50–69 year olds.

Patients and Methods: 846 patients who had tested FOB positive were studied prospectively. The result of each individual's colonoscopy report was accessed and linked to the medication they were taking. This information was then correlated to analyse the effect of anticoagulant medication on the false positive rate. In this study diverticular disease was included as both a positive and negative colonoscopy due to its unknown quantity with regard to occult bleeding.

Results: Of the 846 patients studied 301 (35.6%) were on anticoagulants and 545 (64.4%) were not. A statistically significant 6.4% ($0.02<p<0.05$) more negative colonoscopies (no pathology detected) were found in patients taking anticoagulant medication. When

diverticular disease was considered as a ''negative colonoscopy'' this figure remained significant with an 8.3% difference ($0.01<p<0.02$) between positive and negative colonoscopies. Finally, patients on anticoagulants and not on anticoagulants were divided based on whether they exhibited non-neoplastic disease (negative colonoscopy) or neoplastic disease (positive colonoscopy). This found a statistically significant 9% difference ($0.01<p<0.02$) between the two negative colonoscopy groups.

Conclusions: A statistically significant difference was found between the population taking anticoagulants and those not with respect to false positive FOB tests. It would therefore appear that anticoagulant medication can increase the false positive rate of the FOB test thus reducing its specificity. Whether an individual testing positive on FOB screening should be retested off such medication requires consideration.

263 USE OF OLIGOFRUCTOSE TO PREVENT ANTIBIOTIC ASSOCIATED DIARRHOEA IN ELDERLY PATIENTS

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Introduction: Antibiotic associated diarrhoea, especially caused by *Clostridium difficile* infection, leads to significant morbidity and mortality in elderly patients. A high faecal bifidobacterial concentration is thought to be a major factor in colonisation resistance against invading pathogens. Oligofructose is selectively metabolised by bifidobacteria and results in a marked increase in their numbers. The purpose of this study was to determine if the incidence of antibiotic associated diarrhoea could be reduced by oral oligofructose.

Methods: Consecutive inpatients over the age of 65 years who were prescribed a broad spectrum antibiotic in the preceding 24 hours were enrolled for the study. They were randomised to receive either oligofructose or placebo in a double blind manner. The test substance was taken while on antibiotics (phase 1) and continued for a further seven days (phase 2). Subjects were followed for a further seven days (phase 3). Throughout the study, subjects were monitored for the development of diarrhoea. On entry to the study a stool sample was sent for culture for *C difficile* and for *C difficile* toxin A. If during the study, diarrhoea occurred, a further stool sample was tested for the presence of *C difficile* toxin A.

Results: Of the 435 patients enrolled, 119 (27%) developed diarrhoea of which 49 (11%) had *C difficile* infection. There was no difference in the incidence of diarrhoea, occurrence of infection with *C difficile*, length of antibiotic prescription or length of hospital stay between the two groups. Oligofructose did increase faecal bifidobacterial concentrations ($p<0.001$; 95% CI 0.99 to 2.00).

Conclusion: Oligofructose increases faecal bifidobacteria concentration but does not protect elderly patients receiving broad-spectrum antibiotics from antibiotic associated diarrhoea due to *C difficile* or otherwise.

264 MICROBIAL DIVERSITY AND CARBOHYDRATE EXPRESSION IN HEALTHY AND NEOPLASTIC COLONIC TISSUE

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Background: Colonic microbiota can influence and modulate the colonic neoplastic process. The microbiota also affect colonic carbohydrate expression, which itself is altered by the neoplastic process. Despite their importance, very few studies have addressed the composition of mucosally associated bacteria and their relationship to carbohydrate expression in the healthy and diseased human colon.

Aims: To define mucosal bacterial populations in healthy and neoplastic human colonic tissue and to correlate this with carbohydrate expression.

Methods: Faecal samples and mucosal biopsies from 6 anatomically distinct colonic sites were taken from two healthy individuals. Bacterial populations were compared using 16S rDNA sequencing and DGGE—a microbial fingerprinting technique. Lectin histochemistry was performed on the 6 colonic sites to determine carbohydrate expression. In addition, DGGE analysis was performed on paired polyp/normal and cancer/normal samples from 30 individuals.

Results: 16S rDNA sequencing and DGGE analysis of the healthy subjects indicated that the bacterial composition of the faecal sample did not reflect that present at the mucosal surface. However, the different colonic sites showed a largely similar microbial cohort across the entire colon. Lectin histochemistry showed differential carbohydrate expression within the colon, with the most marked differences seen between the caecum and rectum. DGGE analysis of the neoplastic/normal pairs showed differences in microbial composition for some but not all pairs. Studies correlating these differences with carbohydrate expression in neoplastic/normal pairs are ongoing.

Conclusion: The demonstration that some polyps harbour a different mucosal microbiota compared with their immediately adjacent normal mucosa may be very relevant to the pathogenesis of colorectal cancer. We speculate that a neoplasia induced change in the carbohydrate expression attracts a different microbiota that may contribute to subsequent carcinogenesis in some polyps.

265 SELDI-MS PROTEIN PROFILING CAN DIFFERENTIATE TUMOUR FROM NORMAL COLORECTAL TISSUE

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Introduction: Surface enhanced laser desorption ionisation mass spectrometry (SELDI-MS) is a technique which has been used to study proteomic patterns in cell lines, tumour material, and serum samples but has yet to be used to examine colorectal cancer tissue specimens. In this study we used this technology to examine the feasibility of differentiating tumour from normal colorectal tissue.

Methods: 210 proteomic spectra were generated from 95 normal and tumour tissue samples. Ciphergen Biomarker Wizard was used to identify significant peptide peaks. In-house decision analysis tree was then used to differentiate the two sample types.

Results: The decision analysis tree was able to differentiate colorectal tumour from normal tissue with a sensitivity and specificity of 83.7% and 87% for tumour and 87% and 83.7% for normal samples respectively.

Discussion: This feasibility study has shown that SELDI-MS protein profiling can distinguish between tumour from normal colorectal tissue with a high degree of sensitivity and specificity.

266 A MULTIDISCIPLINARY APPROACH TO ENTEROCUTANEOUS FISTULAE

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Introduction: Enterocutaneous fistulae (ECF) remain a serious complication of abdominal surgery and even with early control of sepsis, good wound care, and improved nutritional support reported mortality rates still exceed 6–8%.

Aims: To analyse the outcome of patients with ECF treated by a combined intestinal failure team of medical, surgical, specialist nursing, dietetic, pharmacy, and psychological staff.

Methods: A retrospective review was undertaken of the case notes of 191 ECF patients treated between 1992 and 2002.

Results: 159 ECF developed secondary to surgery (83%). Of these, 72 (45%) had IBD and 7 (4%) had undergone previous radiotherapy. 32 cases were unrelated to surgery, 29 of whom had Crohn's disease. Three cases occurred spontaneously. 97 (51%) were from ileum, 32 (17%) duodenum or jejunum, 18 (9%) unclassifiable small bowel, 36 (19%) colonic, 1 (0.05%) stomach, and seven (4%) of unknown source. 20 (10%) patients had laparostomy wounds. 65 (34%) ECF were high output (>500 ml/24 hrs). 94 (50%) patients required total parenteral nutrition (median duration 5 weeks). 11 (6%) had enteral feeding via nasogastric tube, and 1 via gastrostomy.

125 patients received definitive resectional surgery. 84 healed after 1 operation, and 17 healed after further surgery, to give a closure rate of 101/125 (81%). 11 patients had surgery to drain sepsis only and 8 of these ECF healed (closure rate 8/11 73%). Of the 55 patients managed non-operatively, closure occurred in 34 (61%). Six fistulae closed after an initial defintive operation followed by refistulisation and then conservative management. The total closure rate was therefore 149/191 (78%). There were 12 deaths due to fistulae related complications (mortality rate 6.3%). All were due to sepsis. Four occurred during hospitalisation, 6 at home, 1 after transfer to another hospital, and 1 on readmission with fistula related aorto-bifemoral bypass graft infection. Six patients died of unrelated causes but with persisting fistulas.

Conclusion: A specialist multidisciplinary approach yields healing of the majority of fistulae (78%), but mortality rates remain high at 6.3%.

267 HISTOPATHOLOGICAL AND CLINICAL EVALUATION OF SERRATED ADENOMAS OF THE COLORECTUM

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Aims: To evaluate the diagnostic utility of the histological characteristics ascribed in the literature to serrated adenomas, and to develop a practical working model to allow its reliable identification. We will also document the frequency and location of serrated adenomas identified in an unselected series of individuals undergoing colonoscopic evaluation, as well as the clinical characteristics of those individuals.

Patients and Methods: 140 consecutive individuals (the prospective polyp dataset) (97 male, 43 female, age mean 63.3y, range 29–98y) with 255 polyps were identified from 919 individuals undergoing colonoscopy. Further polyps were added for the purpose of histological comparison from these individuals over a six year period (extended polyp dataset, n=380). The architectural and cytological features of each polyp in this dataset were then independently assessed by two examiners in a blinded fashion for eight selected histological characteristics.

Results: In the prospective polyp dataset, 56 patients had 72 hyperplastic polyps, 9 had 13 serrated adenomas, and 98 had 170 conventional adenomas. There was no difference in the age, sex, or cancer association of the nine patients with SA when compared with other individuals with polyps. The prevalence of SA was 9/919 (1%) in our population with an average size of 5.4 mm (SD 2.50). When assessing SA histologically, the combination of nuclear dysplasia and glandular serration of at least 20% provided the most accurate model for detection of SA (sensitivity 100%, specificity 99%). Other criteria provided supportive evidence but did not increase the diagnostic yield.

Conclusion: The optimum model for the histological identification of the serrated adenoma includes the presence of a serrated architecture in at least 20% of glands in association with nuclear dysplasia.

268 SHOULD COLONOSCOPY BE THE INITIAL INVESTIGATION TO ASSESS LARGE BOWEL SYMPTOMS?

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Introduction: Double contrast barium enema (DCBE) with rigid or flexible sigmoidoscopy is widely used as the initial investigation in patients with large bowel symptoms due to ready availability, safety, and perceived cost advantages. Colonoscopy is often reserved for patients with persisting symptoms after DCBE.

Methods: We analysed the symptoms and DCBE reports of all patients who underwent DCBE between June 2002 and November 2002. The symptoms in 52 males and 89 females were altered bowel habit (79), abdominal pain (89), rectal bleeding (61), nausea and vomiting (41), weight loss (38), diarrhoea (23), anaemia (12).

Results: 34 DCBE were reported as suboptimal due to poor preparation, patient intolerance, and severe diverticular disease. Of the 106 satisfactory examinations, 8 required follow up management (1 cancer, 2 suspected cancers, 3 had polyps, and 2 had suspect inflammatory bowel disease). In total 41 patients were considered for follow up colonoscopy based on the reports.

Basic cost of colonoscopy is comparable to the combined cost of flexible sigmoidoscopy and DCBE. The additional 41 repeat procedure in the DCBE group would significantly increase the financial burden. Additionally, the number of bowel preparation taken is also higher in the DCBE group. Furthermore, based on the symptoms (bleeding and diarrhoea) a significant proportion would benefit from direct visualisation of bowel mucosa and biopsy.

Conclusion: Colonoscopy is cost effective, less onerous and is potentially therapeutic. Therefore, more resources should be directed to improving the provision of colonoscopy.

269 NEUROMYOGENIC PROPERTIES OF α-2 ADRENOCEPTORS IN ISOLATED INTERNAL ANAL SPHINCTER

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Introduction: Topical application of phenylephrine, a selective α_1-adrenoceptor agonist increases anal sphincter pressure in subjects with passive faecal incontinence, but its potential use is limited by local side effects. We have examined the effect of brimonidine, a selective α_2-adrenoceptor agonist used for treating glaucoma, on myogenic tone and neurogenic responses in isolated sheep internal anal sphincter (IAS).

Methods: Using a validated model, strips of sheep IAS were prepared for isometric tension recording. Each preparation was electrically stimulated at 1 Hz and 10 Hz for 30 s (300 mA pulses, 0.3 ms duration) in the absence and presence of brimonidine. This was repeated following pretreatment with 0.3μM RX-811059, a selective α_2-adrenoceptor antagonist. Responses are shown as the mean (SEM).

Results: Brimonidine (0.3μM) increased baseline myogenic tone by 33 (6.6)% (n=10), which was reduced to 5.1 (1.2)% (n=8) following pretreatment with 0.3μM RX-811059. Electrical field stimulation caused neurogenic relaxations of similar magnitude at 1 Hz, 49.9 (8.1)%, and 10 Hz, 54.5 (5.0)%, (n=10), but of different time course; the time to 50% recovery of response after stimulation (t_{50}) was 3.7 (1.2) s and −8.2 (2.2) s, respectively. In the presence of 100μM L-NAME, an inhibitor of nitric oxide synthase, the neurogenic response to 1 Hz was abolished and the response to 10 Hz converted into a contraction. Following exposure to 0.3μM brimonidine the magnitude of the responses to 1 Hz , 53.6 (6.1)%, and 10 Hz, 64.2 (6.4)%, were not altered, but the duration of the response to 10 Hz was significantly increased, t_{50} 0.7 (1.9) s, ($p<0.05$). The latter effect of bromonidine was not observed in the presence of 0.3μM RX-811059, t_{50} −6.4 (4.0) s.

Conclusion: We have demonstrated the presence of both post and prejunctional α_2-adrenoceptors on sheep IAS. The former increases myogenic tone, while the latter enhances nitric oxide mediated neurogenic relaxations. Local application of brimonidine may be useful for treating passive faecal incontinence.

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270 INCREASED INTRAEPITHELIAL LYMPHOCYTES IN DUODENAL BIOPSIES WITH NORMAL VILLOUS ARCHITECTURE: CORRELATION WITH CLINICAL FINDINGS

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Introduction: In recent years it has been claimed that increased intraepithelial lymphocytes (>40 IELs/100 enterocytes) with normal villous morphology is the first and most sensitive marker of the effects of gluten on small bowel mucosa and often it is the only abnormality.

The aim of this study was to investigate the correlation between this histological finding in duodenal biopsies and the clinical findings and follow up of these patients.

Method: Duodenal biopsies with this histological finding were retrieved and the IEL counts were reviewed using CD3 immunostain, including only cases with counts >40 IELs/100 enterocytes. Patient records were reviewed retrospectively.

Results: 37 patients investigated between 1999 and 2002 were identified with a median age of 47 years (range 3–86); 31 were investigated for upper gastrointestinal symptoms; 34 were found to be iron deficient; 2 had dermatitis herpetiformis and 1 had a family history of coeliac disease. Endoscopy was normal in 31 patients; 5 had gastritis and 1 a gastric ulcer. None had macroscopic duodenal abnormalities. At initial duodenal biopsy all had >40 IELs/100 enterocytes with normal villous morphology. Positive serum antibody titres were present in 53%: antigliadin in 11/28 (39%) and antiendomysial in 4/28 (14%). 2/28 (7%) had prolonged prothrombin time; 8/28 (29%) had abnormal iron studies; 1/13 (8%) had abnormal serum folate and B12 and 13/33 (39%) had raised serum transaminases. Only 8/37 were placed on a gluten free diet (GFD) but 7/8 (87%) responded clinically with a decrease in IELs confirmed in a subsequent biopsy in 5/7 patients.

Conclusion: Increased IELs with normal villi appears to be a significant marker of gluten sensitivity but additional prospective studies with trial GFD and clinicopathological follow up are needed.

271 VALUE OF ENDOMYSIAL ANTIBODY IN SELECTING TTG POSITIVE PATIENTS FOR DUODENAL BIOPSY

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Introduction: The IgA anti-tissue transglutaminase (TTG) assay is becoming the preferred initial screening test for coeliac disease because it is less labour intensive than the more specific endomysial antibody assay (EMA). Our laboratory therefore confirms all positive TTGs with EMA. We examined the clinical impact of this practice before and after a recalibration of the TTG assay by its manufacturer.

Methods: We reviewed duodenal biopsies performed for patients with positive TTG assays during six months of 2001 and six months of 2002. Histological results were correlated with TTG titre and EMA results. A positive TTG was taken as a result exceeding 10 units/ml.

Results: During the 2001 period 61 patients had positive TTG of whom 29 underwent biopsy. Coeliac disease was confirmed in 15, of whom 14 were also EMA positive. Biopsies in three other patients were equivocal, showing normal villi with increased intraepithelial lymphocyte counts. Biopsies of 11 patients were confirmed normal, and EMA was negative in all patients in this group. TTG titres were median 23.5 units/ml (range 10.3 to >200) in those with normal histology.

After these findings the manufacturer of the TTG assay amended the calibration curves. In the following 6 months 56 patients had positive TTG of whom 26 had biopsy. Coeliac disease was confirmed in 21, all of whom were EMA positive. Five others had normal histology; of these, four had TTG titres 10–20 units/ml but all four were negative by EMA. One patient with normal histology was strongly positive by both EMA and TTG.

Conclusion: Even after optimisation of the TTG assay, confirmatory testing by EMA increases the overall specificity of serological testing for coeliac disease. Unless the diagnosis is suspected clinically, biopsy can be avoided in patients with low TTG titre and negative EMA.

272 SHOULD WE BIOPSY PATIENTS WITH RAISED ANTIBODIES AGAINST TISSUE TRANSGLUTAMINASE

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Introduction: The introduction of an immunoassay measuring antibodies against tissue transglutaminase (tTG) has changed the investigation of patients with potential coeliac disease (CD) and is widely used by both GPs and gastroenterologists. Before this anti-endomysial antibodies (EMA) were measured as a screening test. This test was hard to reproduce and required patients to undergo gastroscopy and small bowel biopsies (SBB) to confirm the diagnosis. With a more reproducible test could SBB be avoided?

Aim: To investigate whether patients with a raised tTG (>10 units) need to have small bowel biopsies to confirm the diagnosis of CD.

Results: 1503 tests were done in 15 months (range 0–>300 U). 4 patients refused SBB but responded to a gluten free diet. All patients with tTG>30 had CD. 19 (23% of positive tTG pts) were EMA negative. 8/12 patients who were EMA negative were positive for CD. 15/19 EMA negative patients had levels of tTG—that is, 10–30. This situation has been addressed. Those patients (n=1429) with a negative result for tTG—that is, <10 only 186 (13%) had had SBB. No new diagnoses of CD in this group.

Conclusions: In our practice patients with a raised tTG>30 have CD and could avoid SBB. Patients with a tTG <10 do not have CD and therefore biopsying is unnecessary except to diagnose other conditions. There is an indeterminate group with a mildly raised tTG (10–30 units) where SBB are still essential. Negative EMAs should not stop SBB if the diagnosis of CD is raised.

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	tTG<10	tTG(10–30)	tTG>30
Total	1421	32	50
Not biopsied	1235	14	7
New coeliac	0	16	43
Normal	169	3	0
Other diagnosis	17	0	0

273 SCREENING OF RELATIVES OF PATIENTS WITH COELIAC DISEASE

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Background: First degree relatives of individuals with coeliac disease are thought to have a 10% chance of also being affected. This higher prevalence might suggest that screening relatives of coeliac patients would be beneficial in identifying undiagnosed cases of coeliac disease. A percentage of coeliac patients have either IgA deficiency or have negative IgA antibody tests. Therefore an IgA quantification or additional IgG based antibody test is required when screening.

Methods: We screened 725 relatives of patients with CD. 586 were first degree relatives and 139 second degree relatives. We screened using ELISA for IgA and IgG anti-tissue transglutaminase (tTG) antibodies. All IgA-tTG positive sera were then tested for IgA-EMA. All IgG-tTG positive sera, with negative IgA-tTG, were tested for total IgA and IgG_1-EMA. We have assumed that any individual with positive IgA-EMA is likely to have coeliac disease and requires a duodenal biopsy.

Results: We identified 35 new patients (4.8% of those screened) in the screening of all affected families. 33 of these cases were in the 586 first degree relatives (5.6%) screened and 2 were in the 139 second degree relatives (1.4%). Two of these new patients were IgA deficient (5.7%), and 2 (5.7%) were IgG_1-EMA positive in the absence of IgA-EMA or selective IgA deficiency. Thus 4 patients (11.4%) would not have been identified using an isolated IgA-EMA test. We are currently seeking confirmation of coeliac disease in these patients by small bowel biopsy before and after a gluten free diet.

Conclusions: We therefore recommend an algorithm for screening of first degree relatives of patients with coeliac disease. Screening for coeliac disease in such individuals should include at least one IgG based screening test. Second degree relatives would not appear to have an increased prevalence of coeliac disease.

274 AN ESTIMATE OF THE SIZE OF THE ''SUBMERGED COELIAC ICEBERG'' IN A WELL DEFINED DORSET POPULATION

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Introduction: Studies of population serological screening for coeliac disease (CD) have identified numerous undiagnosed cases, leading to the concept of a ''coeliac iceberg''. We sought to estimate the proportion of undiagnosed cases in a well defined local population, by comparing an estimate of point prevalence derived from incidence data with published estimates of overall disease prevalence.

Methods: Clinical and demographic data for all biopsy proven incident cases of CD diagnosed at Poole Hospital (PH) during a ten year period from 1993 to 2002 were collected prospectively. There was no formal screening programme for CD during this time. To minimise referral bias, the study area was defined by a line joining all points lying one third of the way between PH and the nearest adjacent hospital. Only cases residing within this area at diagnosis were included in the study. Population statistics were obtained from the UK Census 2001. Age specific incidence was calculated and point prevalence estimated.

Results: The defined study area provided a total population of 183 699 and contained 159 incident cases of CD (mean age 51 years). Overall incidence (cases/100 000/annum) was 8.7 (95% CI 7.4 to 10.1). Age specific incidence ranged from 2.5 (1.1 to 4.9) in 0–14 year olds to 16.8 (12.4 to 22.3) in 60–74 year olds. Assuming a steady annual incidence of CD and a mean life expectancy from diagnosis of 30 years, the point prevalence of biopsy-proven CD can be estimated at 0.3%.

Discussion: These data confirm that the age specific incidence of CD is some sixfold greater in later life than in childhood. Studies of serological screening in European populations (Catassi 1995, Johnston 1998) have estimated an overall CD prevalence of 0.5–1%, with a ratio of undiagnosed to diagnosed cases of about 6.5:1. Assuming a similar overall prevalence, our estimated point prevalence for diagnosed CD of 0.3% suggests a rather lower ratio of 2:1 or less in the local population. This may weaken the argument for population screening.

275 PERCENTAGE OF ENERGY OBTAINED FROM MAJOR FOOD GROUPS BY COELIAC PATIENTS ON A STRICT GLUTEN FREE DIET

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Background: A strict gluten free diet (GFD) is the recognised treatment for patients diagnosed with coeliac disease (CD). As food prohibited to patients with CD has a high proportion of complex carbohydrates, there may be excess consumption of fats and proteins (with a decrease in carbohydrates) and thus an increase in energy consumed. There are limited data available on the diets of adult patients in the UK on a strict GFD. Significant differences would have implications for GFD compliance and current dietetic advice.

Methods: Over an 8 week period, all patients seen in a weekly, specialist gastroenterology clinic in a large UK teaching hospital, with histologically confirmed CD and on a strict GFD were invited to complete prospectively a validated 3 day food diary. 22 patients were identified, of whom 14 returned completed diaries. Completed diaries were inputted into ''Microdiet Plus for Windows v1.1'', a computerised nutrient databank. Data for gluten free foods not in the nutrient databank were obtained from ''Gluten-Free Booklet 2003'' published by the British Dietetic Association. Results obtained were compared against the ''National Diet and Nutrition Survey of Adults 19–64'' published in July 2003 by the Office for National Statisitics.

Results: Mean age of respondents was 54.2 years (range 34–73). 12 out of the 14 patients were female. Overall, 38% of energy was obtained from fats, 48% from carbohydrates and 14% from protein. This compares with 34% from fats, 49% from carbohydrates and 17% from protein in a representative population from Northern England. These differences were not significant. Average (SEM) energy intake for the 2 males was 8.37 (0.55) MJ/day (2003 (92.3) kCal/day), cf. 9.72 (0.09) MJ/day (2313 (20.2) kCal/day) in the representative population and 9.22 (0.57) MJ/day (2205 (138) kCal/day), cf. 6.87 (0.06) MJ/day (1632 (14) kCal/day) for the females ($p=0.001$). Average BMI for females was 24.1 (1.31).

Conclusion: Percentage of energy obtained from the major food groups did not differ significantly from the representative population. Female CD patients on a strict GFD have a significantly higher energy intake, but this is not reflected in an increased BMI.

276 POLYMORPHISMS IN THE *MEP1A* GENE ARE NOT ASSOCIATED WITH SUSCEPTIBILITY TO COELIAC DISEASE

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Background: Meprin α is an endopeptidase from intestinal epithelial cells that accumulates at the brush border membrane and is also secreted into the gut lumen. In the small intestine, meprin α is co-expressed with a highly similar isoform, meprin β. It cleaves and has the potential to modify a wide range of luminal gut proteins including gliadin. *MEP1A* is located at 6p11–12 in proximity to the HLA region, which has been widely replicated as a susceptibility locus for coeliac disease. Genome wide scans have also demonstrated a susceptibility locus at 6p12 with a heterogeneity lod score >2.

Aim: Identify *MEP1A* polymorphisms (SNPs) and test for association with coeliac disease.

Methods: Mutations were detected by directly sequencing (ABI 3700) DNA samples from 12 coeliac, 6 NOD2 negative CD, and 6 UC patients. Association with disease was tested in a case control study in 192 coeliac patients and 372 healthy controls.

Results: Out of eleven exonic (8 novel) and 2 intronic variants, six exonic variants (four common) were sequence genotyped. The sample size had enough statistical power to analyse the 4 common exonic SNPs and 1 twelve base pair insertion. SNP1 allele frequencies: HC 35.1% *v* coeliac 35.3% ($p=0.94$); SNP2: HC 3.3% *v* coeliac 2.4% ($p=0.42$); SNP3: HC 57.6% *v* coeliac 60.9% ($p=0.34$); SNP4: HC 25% *v* coeliac 27.7% ($p=0.40$); SNP5: HC 61% *v* coeliac 64.3% ($p=0.32$); 12bp insert: HC 60.3% *v* coeliac 64.5% ($p=0.22$).

Conclusions: No significant associations were found between the meprin α gene locus and coeliac disease, which however does not exclude an association of meprin β with coeliac disease.

277 NATURAL ANTIBIOTIC EXPRESSION IN COELIAC DISEASE—CORRELATION WITH VILLOUS ATROPHY AND RESPONSE TO GLUTEN FREE DIET

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Background: As infection might influence the pathogenesis and presentation of coeliac disease, we aimed at investigating the expression of epithelial natural antibiotics and the influence of gluten free diet in this condition.

Methods: Twenty three subjects were studied: 10 controls and 13 with newly diagnosed coeliac disease, with a median age of 46 years. Distal duodenal biopsies were taken at baseline and after a median of 6 months of starting gluten free diet. The specimens were assessed by histology, and by real time quantitative polymerase chain reaction for the expression of constitutive and inducible natural antibiotics. These included human α (HD5) and β defensins (HBD1, HBD2) and secretory leukocyte protease inhibitor (SLPI). All specimens carried code numbers for blind assessment.

Results: The epithelial HBD1 in subjects with coeliac disease had a median of 0.02 at baseline compared with 0.34 in controls ($p<0.001$). It correlated negatively with the degree of villous atrophy ($r=-0.64$; $p=0.019$), and rose to 0.04 after taking gluten free diet ($p=0.035$). The post diet levels were still lower than in controls ($p<0.001$). The expression of other natural antibiotics was comparable in the presence or absence of coeliac disease.

Conclusions: The expression of HBD1, a constitutive antibiotic, is low in celiac disease and correlates negatively with the severity of villous atrophy. Its level is significantly, but partially, corrected with gluten free diet. Inducible antibiotics are unchanged. The expression of epithelial natural antibiotics is, therefore, limited in coeliac disease.

278 THE RAPID REPRESSION OF DMT-1 BY THE HEPATIC ANTIMICROBIAL PEPTIDE HEPCIDIN

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Background: Recent evidence suggests that the hepatic antimicrobial peptide hepcidin is the key regulator of small bowel iron absorption. It appears to be induced in response to high body iron stores and the proinflammatory cytokine IL-6. It causes a rapid inhibition of small bowel iron absorption although the enterocyte target for its action is unknown. Here we provide evidence that hepcidin can cause direct repression of the principal enterocyte iron absorption protein, divalent metal transporter 1 (DMT-1).

Methods: Caco-2 cells, an established model for the study of enterocyte function, were challenged for up to 24 hrs with varying concentrations of hepcidin peptide. RNA and protein were extracted and subject to analysis for DMT-1 expression by real time PCR and western blotting, respectively. In addition, Caco-2 cells were co-cultured in the presence or absence of hepcidin for a 24 hr period, after which cells were lysed and immunoprecipitated with antibodies to either hepcidin, DMT-1, iron regulated protein 1 (IREG 1), and transferrin receptor 1. Immunoprecipitates were then subject to proteomic analysis.

Results: Exposure of Caco-2 cells with hepcidin at a concentration of 10 ng/ml resulted in a 30% repression in DMT-1 mRNA ($p<0.05$). This was confirmed at the protein level where a significant repression was observed by 8 hours and sustained for 24 hours. As yet we have been unable to demonstrate any significant immunoprecipitation between hepcidin and the above named iron transporters.

Conclusions: We provide evidence that hepcidin can cause a rapid and significant repression of DMT-1 expression in Caco-2 cells. The signalling mechanism for this direct repression of DMT-1 remains unclear. The proteomic analysis suggests that hepcidin mediated repression of DMT-1 is likely to involve pathways other than the established iron transport molecules. The identification of the molecular targets of hepcidin is likely to lead to a number of therapeutics options in conditions of deregulated iron metabolism.

279 A ROLE FOR TNF-α IN THE REGULATION OF SMALL BOWEL IRON ABSORPTION

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Background: Iron, an essential nutrient, is absorbed in the proximal small bowel via divalent metal transporter 1 (DMT-1). DMT-1 expression is tightly regulated by the body's iron requirements. In this study we demonstrate a modulation of DMT-1 expression by TNF-α, an effect that may have important clinical implications.

Methods: (1) Caco-2 cells were stimulated with TNF-α (5 ng/ml) for up to 24 hrs. DMT-1 mRNA and protein expression was determined by real time PCR (RT-PCR) and western blotting respectively. Localisation of DMT-1 was demonstrated by immunofluorescence. (2) Endoscopic biopsies of normal small bowel (n = 54) were cultured in a 95% O_2 +/−TNF-α for up to 12 hrs and subject to mRNA and protein analysis. (3) Coeliac disease was utilised as an in vivo model of the effects of TNF-α on small bowel DMT-1. DMT-1 mRNA expression was compared between normal and coeliac small bowel (n = 5) by RT-PCR and DMT-1 localisation determined by immunohistochemistry.

Results: (1) Caco-2 cells challenged with TNF-α showed a 10-fold increase in DMT-1 mRNA expression within 1 hour ($p<0.05$). This was further confirmed at the protein level. TNF-α increased cellular expression and membranous localisation of DMT-1. 2) Using ex vivo small bowel cultures DMT-1 mRNA expression increased fivefold in response to TNF-α stimulation for 1 hour ($p<0.05$) and was further verified at the protein level. (3) Coeliac small bowel biopsies showed increased DMT-1 expression, which was aberrantly localised in crypt enterocytes. These effects were independent of serum iron status.

Conclusions: The rapid and marked induction in DMT-1 observed in vitro and in vivo in response to TNF-α would suggest a direct modulation of DMT-1. In coeliac disease the increase in DMT-1 could, in part, be due to small bowel inflammation and may show a protective mechanism against iron deficiency. Finally, treatments aimed at blocking the effect of TNF-α could have potentially deleterious effects on small bowel iron absorption.

280 FASTING PLASMA NITRIC OXIDE PRODUCTS IN COELIAC DISEASE

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Background: Inducible nitric oxide synthase is expressed in the small intestine of patients with coeliac disease. This produces increased plasma concentration of nitric oxide end products (NOx) most marked in those ingesting gluten. The rate of change in NOx over time following the introduction of a gluten free diet (GFD) and its relationship to histology and coeliac serology is unknown.

Methods: A prospective study of 20 newly diagnosed adults with coeliac disease to determine the change over time of plasma NOx following the introduction of a GFD. Fasting plasma NOx was determined by the Greiss reaction at diagnosis and repeated at 2, 4, and 6 months after introducing a gluten free diet. Duodenal biopsies were taken at diagnosis and repeated at 6 months, then graded according to the Marsh classification. Endomysial and gliadin antibodies were checked at 0, 2, 4, and 6 months.

Results: 20 patients were recruited. Median plasma NOx at the start of the study was 77.2 μM (mean 91.5 (SD 16.8) μM, range 23.8–328.2 μM). This value fell rapidly with time. The median value 2 months after the introduction of a GFD was 45.2 μM (mean 58.7 (SD 14.1) μM, range 7.5–258.0 μM), at 4 months it was 39.0 μM (mean 50.9 (SD 13.0) μM, range 3.1–216.1 μM) and the median after 6 months was 16.0 μM (mean 35.4 (SD 10.9) μM, range 5.0–196.1 μM) with statistically significant reductions at 2 and 6 months compared with baseline ($p<0.01$ and $p<0.005$ respectively: Wilcoxon signed ranks). Plasma NOx was correlated with histological grade initially ($p<0.05$: Kruskal-Wallis) but not after 6 months of a GFD ($p = 0.13$). Coeliac serology correlated poorly with histology.

Conclusions: This study confirms increased plasma NOx levels in patients with untreated coeliac disease. Plasma NOx falls rapidly after starting a GFD in coeliac disease and is related to histological grade initially. It continues to fall for at least 6 months.

281 MANAGEMENT OF HIGH OUTPUT STOMAS

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Background: Patients with a high output stoma (HOS) of more than 2000 ml daily, are likely to have complications of dehydration and hypomagnesaemia.

Aim: To review outcome of all HOS patients over 22 months.

Method: Management of HOS includes hypotonic fluid restriction (500–1000 ml daily), administration of an glucose-electrolyte solution (90 mmol/litre Na^+) and further reducing intestinal losses with anti-diarroeal and anti-secretory drugs; loperamide (2–8 mg qds) +/− codeine phosphate (30–60 mg qds) and omeprazole (40 mg od) or octreotide (50–100 mcg bd).

Results: 17% of all ileostomies formed in 2002 were HOS. There were 33 patients (19 male), mean age 59 (32–88). 12 (37%) had cancer, 6 (18%) ischaemia, 6 (18%) inflammatory bowel disease, 6 (18%) perforation, 2 (6%) familial polyposis coli, 1 (3%) other. 24 had loop ileostomies and 4 had <150 cm small bowel remaining. 25 (76%) were referred within 2 weeks of stoma formation. At referral 24 (96%) required intravenous fluids. 8 were referred >6 months after surgery. 6 (75%) had previously received renal dialysis and one patient was admitted with a creatinine level >1000 umol/l).

14 (42%) HOS patients were discharged home without parenteral fluids. 6/14(43%) required readmission due to dehydration, and all had been non-compliant with their hypotonic fluid restriction. 13/14 received oral magnesium oxide and one intravenous magnesium sulphate.

Conclusion: With appropriate management 21/22 (87%) HOS patients were able to stop parenteral fluids. Most HOS patients at home need oral magnesium.

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Outcome	n = 33(%)
Post operation resolved in 2 weeks	9 (28)
Stoma reversed	8 (24)
Requiring ongoing management	7 (21)
Died	6 (18) 2<30 days operation
Unknown	3 (9)

282 LACK OF A SYSTEMIC IMMUNE RESPONSE TO ORAL VACCINATION DOES NOT INDICATE LACK OF MUCOSAL IMMUNITY

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Introduction: Enterotoxigenic *Escherichia coli* (ETEC) is a major cause of traveller's diarrhoea and of childhood mortality in the developing world. Vaccination may be beneficial; we are currently performing trials using genetically modified ETEC strains. Response to oral vaccination is usually assessed by analysis of peripheral blood, but this may not represent mucosal immune responses. We report a comparison of systemic and mucosal immune responses following oral vaccination.

Method: Increasing doses (5×10^7, 5×10^8, 5×10^9 cfu) of a colonisation factor antigen I (CFA-I) expressing ETEC strain were given to 3 cohorts of healthy volunteers. Antibody-secreting cell (ASC) responses were measured by ELISPOT at 0, 7, and 10 days, and serological responses were measured by ELISA at 0, 10, and 28 days. On the 13th or 14th day following vaccination each subject underwent a whole gut lavage (WGL) procedure. This is a well validated and well tolerated method of measuring intestinal protein secretion. The fluid obtained was assessed by ELISA for CFA-I specific and total IgA or IgG production.

Results: Serological responses were found in 2 of 5 volunteers given 5×10^8 cfu, and 2 of 5 given 5×10^9 cfu. ASC responses indicated 3/5 responders to 5×10^8 cfu (1 low titre) and 1/5 to 5×10^9 cfu. However CFA-I specific IgA responses in WGL fluid indicated a response in all subjects except 3 given 5×10^7 cfu. The concentration of specific IgA in WGL fluid increased at higher dose levels ($p = 0.02$), and the concentration was positively correlated with dose (Spearman's $\rho = 0.67$; $p = 0.005$). As expected there was no CFA-I specific IgG response in WGL fluid, nor did total IgG and IgA concentrations significantly differ in WGL fluid in the 3 cohorts.

Conclusion: Measurement of specific IgA responses in WGL fluid is a sensitive method of assessing the mucosal immune response to oral vaccination. Negative ASC and serological results may not imply that an individual has failed to respond to oral vaccination.

283 WIRELESS CAPSULE ENDOSCOPY IN UPPER ENDOSCOPY, PUSH ENTEROSCOPY AND COLONOSCOPY NEGATIVE OBSCURE GASTROINTESTINAL HAEMORRHAGE

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Background: Capsule endoscopy has been shown to be superior to push enteroscopy in the diagnosis of the source of recurrent GI haemorrhage with a negative gastroscopy and colonoscopy. A bleeding source may be detected in up to 68% of patients.

Aim: To report on our experience of capsule enteroscopy in patients with significant GI haemorrhage who had a negative upper endoscopy, colonoscopy, and push enteroscopy. This group of patients may be designated ''true'' obscure GI haemorrhage, as push enteroscopy is now fairly widely available.

Patients: Twenty four consecutive patients (M=14; median age 59 years; range 27–88 years) with obscure GI haemorrhage were included in this study. The patients had significant GI haemorrhage with haemodynamic instability and or Hb<10 g/l. All patients had at least one negative upper endoscopy and colonoscopy up to caecum. Push enteroscopy was performed with a SIF Q240 video enteroscope with 240 cm working length and was negative.

Methods: Wireless capsule endoscopy was performed with the Given M2A capsule after overnight fast. The images were downloaded the following day and the entire recording reviewed.

Results: Adequate and useful video images were obtained in 20 out of the 24 procedures. The capsule remained in the stomach in 3 patients and was retained in a Zenker's diverticulum in 1 patient. The capsule endoscopy was considered diagnostic in 9 patients (36%). Of these 9 patients, 7 patients (28%) had small intestinal vascular lesions, 1 had NSAID induced small intestinal ulceration and 1 had ileal Crohn's disease. In 4 patients (16%) lesions suspicious of a source of haemorrhage in the form of erosions/ulcers without evidence of haemorrhage was seen.

Conclusion: In patients with upper endoscopy, push enteroscopy, and colonoscopy negative GI haemorrhage, wireless capsule endoscopy detected lesions thought to be definite or probable source of haemorrhage in 52% of patients. The majority were intestinal vascular lesions. Wireless capsule endoscopy is a useful diagnostic modality after failed conventional diagnostic endoscopic procedures including push enteroscopy.

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284 NUTRITION SERVICES IN THE NORTHERN REGION OF ENGLAND

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Introduction: Malnutrition is commonly found in hospital inpatients; intervention studies suggest this is an independent and reversible prognostic factor. The King's fund (1992) and RCP (2002) recommend all hospitals have a nutrition team, including a nutrition nurse specialist and a nutrition steering committee. Obesity and associated metabolic syndrome are perhaps the most pressing medical problem in the UK. The Northern Nutrition Network (NNN) has been established to improve nutrition services across the region.

Aims: To discover the nutritional services available and workload of hospitals in the northern region.

Methods: A questionnaire was sent to NNN members at all 14 acute hospitals across the region.

Results: Replies were obtained from all 14 hospitals. Only 3 had functioning nutrition support teams with funded nutrition nurse specialists and only 2 met weekly to discuss individual patients. Only 5 hospitals had nutrition steering committees to determine nutrition policy. Total parenteral nutrition was provided by all but one hospital, 5 centres treating >100 pts/year, 9 hospitals had manufacturing pharmacy provision. HPN was provided by 4 hospitals: 3 hospitals with single patients and one with 9 patients. All hospitals managed patients with gastrostomies with 4 hospitals placing >100/year, 9 hospitals had specific outpatient follow up arrangements for such patients. A dedicated obesity service was provided by 4 hospitals with only 1 hospital providing bariatric surgery. All but 2 hospitals had a screening strategy for malnutrition for admitted patients but only 2 systematically screened outpatients.

Conclusions: Nutrition services in the northern region are still insufficient and under resourced despite nationally agreed targets.

285 A MULTIDISCIPLINARY TEAM ASSESSMENT CAN IMPROVE PEG SERVICE

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Introduction: There is increasing demand for percutaneous endoscopic gastrostomy (PEG) for providing nutritional support to patients with dysphagia. There is a need for proper assessment to select the patients who will benefit from PEG feeding. A multidisciplinary team (MDT) consisting of clinician, endoscopist, dietitian, and speech and language therapist can help in selecting right patients for PEG.

Aim: To assess the effect of MDT assessment on early mortality in patients referred for PEG.

Methods: We introduced MDT assessment for all patients referred for PEG from June 2001. Before this all patients referred for PEG had it done without prior assessment by endoscopy team. Our MDT consists of endoscopy physician, nurse endoscopist, dietitian, and speech and language therapist. In this audit we compare the early mortality in patients who had PEG in the period 2 years prior to MDT with those who had it 2 years after the introduction of MDT assessment. 156 patients had PEG from April 1999 to March 2001 without assessment by MDT. 206 patients were referred for PEG and assessed by MDT between June 2001 and May 2003.

Results: 156 patients had PEG without MDT assessment and the MDT assessed 206 patients. After assessment 74 (36%) patients were thought to be unsuitable for PEG and attempted in 132 patients. It was not possible in 2 patients due to technical problems.130 patients had PEG during this period. In patients who had PEG without MDT assessment, 16 (10%) died within first week and 32 (20%) within 4 weeks. In patients after MDT assessment the first week mortality was 7 (5%) and 4 week mortality was 23 (17.5%). Out of 74 patients not recommended for PEG 14(19%) died within the first week and 42 (56%) died within 4 weeks. Dysphagia recovered in 8 (11%) during stay in hospital. If all patients referred for PEG had it done without prior MDT assessment then 1st week mortality would have been 21 (10%) and 4 week mortality 65 (31.5%). Thus there has been a definite reduction in early mortality by selecting appropriate patients for PEG by prior assessment by the MDT.

Conclusion: MDT assessment helps in selecting the appropriate patients for PEG and thus can reduce the workload and cost.

286 DOES A MULTIDISCIPLINARY NUTRITIONAL SUPPORT TEAM (NST) IMPROVE THE QUALITY OF CARE OF PATIENTS RECEIVING TOTAL PARENTERAL NUTRITION? A TEACHING HOSPITAL PERSPECTIVE

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Introduction: Groups such as BAPEN and ASPEN (British Association/ American Society for Parenteral and Enteral Nutrition) recommend that patients receiving total parenteral nutrition (TPN) should be managed by a multidisciplinary NST. We undertook a series of audits at a teaching hospital to see whether such guidelines are appropriate.

Methods and results: Three prospective audits were undertaken. (1) Catheter related sepsis (CRS) (excluding ITU patients) over 1 year. 226 patients received TPN via 56 triple lumen, 24 tunnelled, 2 PICC (peripheral inserted central) and 224 peripherally placed midline catheters (MCs). Central catheters (n=82) were placed by a mixture of teams and MCs by a nutrition nurse specialist (NNS). CRS rate was 18% (n=10), 42% (n=10), 0%, and 4% (n=9) and duration of feeding 2–22, 9–42, 6–37 days, and 6–30 days respectively in each group. (2) Wastage and recycling of TPN bags over 5 weeks. 446 bags of TPN were issued (mean 12.7 bags/day). Of 344 (77%) used on the Trust's main site, 12 (3.5%) were destroyed and 31 (9%) recycled. (3) Appropriateness of TPN administration over 3 months. 119 patients led to 136 patient episodes; 44 (32%) acute/chronic pancreatitis, 69 (51%) other ward based and 23 (17%) ITU. 7% of referrals resulted in TPN not given, 32% started TPN before review by a NST member and 51% started TPN before dietetic review. Median duration of TPN administration was 9 days (range 0–84). 20% were fed for <5 days and 32% <7 days. 33% of episodes resulted in inappropriate referral or use of TPN.

Discussion: These audits showed that insertion of peripheral MCs by a NNS reduced CRS incidence without reducing potential feed duration, the NST pharmacist coordinated recycling of 9% of bags, (approx saving

£11 000/year) and up to 33% of TPN prescriptions could have been avoided. These results back guidelines that a NST is important in the successful running of a TPN service.

287 MEASUREMENT OF GASTRIC EMPTYING DURING CONTINUOUS NASOGASTRIC FEEDING IN NORMAL SUBJECTS

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Background and Aims: Enteral feed given as a bolus has a half emptying time (t½) of 90 min. No data are available on gastric emptying patterns during continuous nasogastric infusion. The gold standard for measuring gastric emptying (GE) is gamma scintigraphy (GS). GS does not measure gastric secretions and exposes subjects to radiation. Electric impedance tomography (EIT) is a new non-invasive, non-isotopic method which measures both feed and gastric secretions. Our aim was (1) to compare EIT with GS in volunteers and (2) to establish normal patterns of GE during continuous infusion.

Methods: GE was measured simultaneously by EIT and GS in 10 fasted, acid suppressed volunteers. Enteral feed was labelled with ^{99M}Tc-Tin colloid and 5 g NaCl to increase resistivity. An initial bolus of 100 mls was given to identify the region of interest (ROI) representing the stomach, followed by continuous infusion of 100 ml/h for 4 hrs. GE curves were obtained by plotting changes in resistivity (EIT) or number of counts (GS) in the ROI with time.

Results: GE curves were obtained in 10 EIT but only 8 GS studies due to failure to identify the ROI. As GE t½ was not appropriate for continuous infusion, area under the curve was compared and showed agreement in patterns of GE in all 8 subjects. However, the relationship between EIT and GS was not linear and there was no relation between the maximum ($p=0.27$) and minimum ($p=0.24$) volumes measured by each method. Unlike administering a bolus, during continuous infusion a relatively steady volume is achieved which is low in normal subjects.

Conclusions: As EIT and GS measure different components of gastric emptying, volumes in the stomach measured by each method are not directly related, but there is agreement between patterns of emptying and filling. This study provides us with a basis for studies in patient groups.

288 CLINICAL EXPERIENCE OF CHRONIC IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION

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Introduction: Chronic idiopathic intestinal pseudo-obstruction (CIIP) is characterised by a failure of intestinal propulsion in the absence of mechanical obstruction. Patients with CIIP may have characteristic histological, radiographic, or manometric findings. CIIP may be primary, or secondary. Patients present with severe pain, abdominal distension, vomiting, and constipation.

Methods: Data were collected by retrospective case note analysis in 50 patients with CIIP referred for specialist nutritional care and management at Barts and The London. This established histological findings, radiographic appearances, and manometric results.

Results: The male to female ratio was 9:41. The range of age at onset (in years) was <1 to 63 (median 25). Five were secondary to scleroderma. 30 of the remaining 45 patients had interpretable full thickness intestinal biopsies; 13 classified as myopathy, 5 as neuropathy, and 12 as normal. Prolonged intestinal manometry had been attempted in 30 patients; 3 interpreted as myopathy, 8 as neuropathy and in 7, attempts at small bowel intubation repeatedly failed. In 4 of this latter group, histology showed a myopathy, 1 a neuropathy, 1 was normal and no biopsy had yet been performed in the other. Barium follow through or CT results were available in 39 patients of whom 19 had dilatation of the proximal small bowel. In those patients without dilatation, 4 had definite histological evidence of myopathy and 2 of neuropathy. Of the 12 patients with normal histology, 8 presented with pain as the first symptom, and required opiate analgesia. Manometry was abnormal in 4 with one failed intubation, 3 were normal, and 4 not done. Mortality was highest in those with normal histology (5/12), while in the whole series it was 11/50. Home parenteral nutrition (HPN) was required in 19, 7 of whom had normal histology; 18 required enteral supplementation.

Conclusion: CIIP is difficult to classify clinically and diagnosis may depend upon several investigations. Patients with normal histology but abnormal manometric or radiographic findings often present with pain first, are more likely to need HPN and may have a high mortality.

289 QUALITY OF LIFE IN CHRONIC IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION

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Introduction: Patients with chronic idiopathic intestinal pseudo-obstruction (CIIP) often suffer severe pain, vomiting, constipation, and abdominal distension. There are currently few data published on the quality of life (QoL) of this patient population.

Methods: Of a series of 40 patients under care at Bart's and the London, 23 patients (20F, 3M) (mean age range 40–48) with CIIP were successfully contacted and asked to complete (a) SF36 (b) hospital anxiety depression (HAD) telephone questionnaires in order to determine QoL and psychological profiles by a single researcher (AC).

Results: Mean anxiety score was 7.70 with 5 patients giving a score of 11 or more. Mean depression score was 7.35 with 4 patients having a score of 11 or more (scores below 7 are normal and 11 or more are highly likely to be clinically significant). The SF36 is divided into 8 domains namely physical function, physical role, general health, vitality, social function, mental health, bodily pain, emotional role. Data for the normal healthy population are supplied by sex and age group. The table gives the results of physical role, general health, and mental health (standard deviation in parenthesis) which proved to be of most interest in this series and compares patient data with normative data in the three largest age/sex groups in this series.

Conclusions: About a fifth of patients have clinically significant anxiety and a sixth depression. Physical role and general health scored much lower than normal whereas mental health scores were much closer to the norm.

290 FISH OIL AND ANTIOXIDANTS ALTER COMPOSITION AND FUNCTION OF CIRCULATING MONONUCLEAR CELLS IN CROHN'S DISEASE

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Background: Cytokine production by peripheral blood mononuclear cells (PBMC) may contribute towards altered bone turnover and other extra-intestinal manifestations of Crohn's disease (CD). Dietary supplementation with eicosapentaenoic (EPA) and docosahexaenoic (DHA) acid rich fish oil influences cytokine production by PBMC in healthy subjects and show therapeutic effects in CD. We therefore investigated the effect of fish oil (and antioxidants) on PBMC incorporation of fatty acids and production of tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and prostaglandin E_2 (PGE_2) in CD.

Design: A randomised controlled trial of fish oil (2.7 g/d of EPA and DHA) and antioxidants (vitamin A, C, E, and selenium) ($n=31$) or placebo ($n=31$) for 24 weeks in CD patients with raised biochemical

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	Physical role		General health		Mental health	
Age group	Normal	CIIP	Normal	CIIP	Normal	CIIP
35–44	87 (2)	12 (18)	72 (20)	39 (29)	70 (18)	75 (14)
45–54	84 (22)	4 (10)	70 (20)	22 (18)	71 (18)	47 (17)
55–64	77 (27)	16 (14)	67 (22)	28 (9)	71 (19)	62 (13)

markers of inflammation (CRP>6.9 or ESR>20). Exclusion criteria included steroid use within the previous 4 weeks. Fatty acid composition was measured by gas chromatography. Cytokine production by PBMC was measured by ELISA following stimulation with Con A and LPS that stimulate T cells and monocytes, respectively.

Results: Fish oil and antioxidants were associated with increases in EPA and DHA incorporation in PBMC ($p<0.01$); and reduced production of IFN-γ by Con A-stimulated PBMC ($p=0.012$) and reduced production of PGE_2 by LPS-stimulated PBMC ($p=0.047$).

Conclusions: Dietary supplementation with 2.7 g/d of EPA/DHA, as fish oil, and antioxidants, modifies PBMC composition and production of PGE_2, by circulating monocytes/macrophages, and IFN-γ, by circulating T cells. The response of extra-intestinal manifestations of CD to dietary fish oil should be investigated in a randomised controlled trial.

291 ''ANOREXIA OF AGEING'': ARE GUT HORMONES THE ANSWER?

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Introduction: The gut hormone pancreatic polypeptide (PP) is synthesised in the pancreas and nerves of the enteric plexus. It is released in response to food ingestion and contributes to the sensation of satiety. Fasted levels of PP increase with advancing age and it has been suggested that PP may contribute to the ''anorexia of ageing''.

Materials and Methods: Blood was collected 2 hourly for 14 h from 9am in 22 healthy volunteers aged between 18 and 80 years. Plasma was prepared immediately by centrifugation and PP concentration determined by radioimmunoassay. All volunteers ate standardised meals at 1 pm and 5 pm. The area under the curve (AUC) was used as a measure of total PP secretion over the day.

Results: The total PP secretion during the day was higher in older people ($r=0.46$ and $p=0.038$). At the majority of time points, including all of those after eating, there was a positive correlation between plasma PP concentration and age. PP concentrations were not affected by sex or *Helicobacter pylori* infection.

Discussion: In addition to the increase in fasted PP with advancing age, we have shown that ageing is associated with higher PP concentrations throughout the day. Total daytime pancreatic polypeptide secretion also increases with advancing age. High pancreatic polypeptide concentrations, particularly after meals, could reduce food intake in older people and potentially contribute to the unexplained weight loss seen in many older people.

292 AUDIT OF TREATMENT PATHWAY AND QUALITY OF LIFE FOR COMMUNITY PATIENTS WITH PEGS

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Background: Patients with percutaneous endoscopic gastrostomies (PEGs) and their carers require training and ongoing support. For many patients little is known of the effect of a PEG on quality of life (QOL).

Aim: To audit the treatment pathway and QOL for patients who have been discharged to the community with a PEG.

Method: Separate questionnaires were sent to patients with PEGs, their principal non-professional carers and to any professional carers—for example, nurses. Only patients whose PEGs were inserted within the local NHS Trust were selected. Questions covered education and support given pre and post PEG insertion and the effect of the PEG on QOL.

Results: 53 questionnaires were returned for 34 patients (age range 20–94 yrs, median 71). The indication for PEG was a CVA in 20 patients (59%). Questionnaires were completed by 14 patients, 21 non-professional carers, and 18 professional carers. 13 patients (93%) and 20 non-professional carers (95%) remembered being consulted about the need for a PEG and 13 (93%) and 21 (100%) respectively understood the reason for PEG insertion. Only 5 patients (36%) and 12 non-professional carers (57%) remembered being told about the risks of PEG insertion. Where relevant, 11 of 12 patients and 15 of 17 non-professional carers were confident about food administration before hospital discharge. All 34 patients had been visited at home either by dietitians (33), GPs (31), or district nurses (19). 14 of 34 patients had had a problem with either the PEG or pump, the delay for resolution ranging from 1 hour to 12 months (median 1 day). Five of 14 (36%) patients and 13 of 21 non-professional carers (62%) thought that the PEG had improved the QOL for the patient, while 2 (14%) and 1 (5%) respectively thought that QOL had worsened. 12 patients (86%) and 19 non-professional carers (90%) would have chosen or advised PEG insertion again.

Conclusion: Education and training in hospital and support within the community were satisfactory. There needs to be more explanation of the risks of PEG insertion and speedier resolution of some problems, but PEG insertion did not worsen quality of life for most patients.

293 PROTON PUMP INHIBITORS ARE ONLY EFFECTIVE IN THE SHORT TERM FOR PREVENTING PEG SITE EXCORIATION

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Introduction: Percutaneous endoscopic gastrostomy (PEG) is the most common route of long term enteral nutrition. An overall morbidity rate of 10–20% is associated with PEGs. A significant component of PEG morbidity is insertion site excoriation that results from gastric fluid contact with skin around the PEG placement site.

Aim: To assess the prophylactic use of multi-unit pellet system proton pump inhibitors (PPI) in PEG feeds to prevent acid reflux onto PEG placement site skin.

Methods: A randomised, prospective, double blind, placebo controlled trial. 42 patients undergoing PEG placement were randomly assigned to receive placebo or 40 mg esomeprazole multi unit pellet system (MUPS) via the PEG from time of PEG placement to day 30. At day 3, 10, and 42 the PEG site was inspected and photographs taken.

Results: 21 patients received drug and 21 received the PPI. At day 3, 20% of patients in the drug group had an event (excoriation >1 cm) compared with 30% in the placebo group (relative risk reduction 33% at 3 days, number needed to treat 10). At day 10, 47% in the drug group and 43% in the placebo group had an event. At day 42, 30% of the patients had been lost to follow up. Of the remaining, 2 patients in the drug group and 1 patient in the placebo group had events.

Conclusion: There was a positive benefit in excoriation reduction in the patients receiving esomeprazole 40 mg at day 3. Both groups had a similar event rate at 10 and 42 days. The main benefit of PPIs for PEG feeds is seen at 3 days and by day 10 this benefit is no longer observed. The use of PPIs following PEG placement is therefore associated with morbidity reduction over the short term but from our study does not appear to be advantageous for sustained use.

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294 LOW DOSE ASPIRIN—AN ASSESSMENT OF PREVALENCE OF USE AND GASTROINTESTINAL RISK PROFILE

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Introduction: Policies to minimise adverse events with NSAIDs have been widely disseminated. Aspirin is associated with lower relative risk of inducing mucosal injury but its use in medical patients is increasing.

Aims: (1) To establish the prevalence of aspirin, NSAID, and COX2 inhibitor use in general medical patients admitted to secondary care. (2) To assess the rates of adverse gastrointestinal events for each group.

Methods: A prospective, proforma based study. Ward pharmacists screened all medical admissions for current or recent aspirin, NSAID, or COX2 inhibitor use. Demographic details, relevant past medical history, drug history, and laboratory results were recorded. All take home scripts and endoscopy referrals were reviewed to minimise ''missed'' cases.

Results: 133 (39.6%) out of 336 consecutive patients (74 male, 59 female) were taking one or more of these medications. Aspirin use (120 (35.7%))—93% low dose—was significantly greater than either NSAID (23(6.8%)) or COX2 inhibitors (12 (3.6%)). Details of each group are in the table. Use of prophylaxis was greater in patients with combined rather than lone treatment ($p=0.05$) or a past history of peptic ulceration ($p=0.01$). In patients taking aspirin alone, the presence of two or more risk factors resulted in increase risk of both GI bleed (3.2% *v* 2.9%) and anaemia (19.4% *v* 8.8%) (χ^2, $p=0.02$ for both comparisons).

Conclusions: (1) Aspirin is a more common cause of upper GI bleed and anaemia in general medical patients than NSAID or COX2 inhibitors. (2) Patients taking aspirin tend to be elderly with a greater degree of comorbidity. (3) GI prophylaxis in patients taking low dose aspirin may be warranted if two or more background risk factors are present.

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	Number (%)	Mean age (range)	Comorb (%)	GI bleed (%)	Anaemic (%)	PPI
Aspirin (A)	98 (74)	71.3 (34–94)	79 (86.8)	3 (3)	15 (15.3)	20 (20)
NSAID	7 (5.3)	56.4 (42–75)	3 (42.9)	1 (28.6)	2 (28.6)	1 (16.7)
COX2I	6 (4.5)	57.1 (48–81)	5 (83.3)	0	0	3 (50)
A+NSAID	16 (12)	68.8 (46–89)	13 (81.3)	1 (6.3)	3 (18.8)	5 (31.3)
A+COX2I	6 (4.5)	63.5 (50–81)	6 (100)	0	1 (16.7)	3 (50)

295 OUTCOME OF ACUTE UPPER GASTROINTESTINAL BLEEDING POST IMPLEMENTATION OF A PROTOCOL BASED MANAGEMENT IN A DISTRICT GENERAL HOSPITAL

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Introduction: Patients with acute upper gastrointestinal bleeding (AUGIB) fall into 2 groups: (1) those with high risk of death in whom aggressive management may reduce the mortality and (2) those with little risk of death who can be discharged early to reduce in-hospital healthcare costs. Education of junior doctors who admit these patients on general medical take for early risk stratification and optimal care is important to achieve these goals.

Methods: A novel clerking proforma, which incorporated evidence based guidelines, and prompts for optimal assessment, referral to endoscopy and patient care was introduced in our hospital. Patients admitted with AUGIB from September 2001 to August 2003 were studied. Episodes that did not require endoscopic assessment were excluded. If the patient had more than one admission for AUGIB, either the first admission or that closest to death was included for core analysis.

Results: There were 462 episodes in 401 patients. Age: 16–101 years (mean 62.1). Male:female = 1.79:1. Inpatient bleeds 9.2%. Drug usage: aspirin 31.2%; NSAID 17.2%; anticoagulants 6.9%. At least one significant comorbidity was present in 68%. The source of bleeding included peptic ulcer (26.2%), varices (6%) and malignancy (2.7%). Other endoscopic lesions such as erosions, oesophagitis, Mallory Weiss tear, etc were seen in 64.8% whereas no source was detected in 22.4%. Where signs of recent haemorrhage were detected (63.8% of peptic ulcers and 87.5% of varices), appropriate endotherapy was carried out. 43 patients had 2nd inpatient gastroscopy for elective 2nd look (46.5%), re-bleed (25.6%) or suboptimal 1st endoscopy (18.6%). All cause inpatient mortality was 8.5%. 53.1% were discharged appropriately and safely, most with in a day of admission. 23.6% stayed longer due to concurrent illness or social reasons. Only 5.5% of patients stayed longer than required.

Conclusion: A protocol based management of AUGIB can result in reduction in in-hospital stay but only a modest reduction in mortality.

296 A DEDICATED OPEN ACCESS GASTROINTESTINAL BLEEDING UNIT—A 10 YEAR PERSPECTIVE

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Introduction: The GI bleeding unit has served the adult population (458 536) of Grampian and the Northern Isles since October 1991. This high dependency unit accepts all with suspected GI haemorrhage and operates a strict management protocol facilitating rapid admission, assessment, and treatment.

Objective: To identify the changes in referral patterns, demography, and clinical management that influenced outcome over 10 years.

Method: Data were collected prospectively and stored in a Microsoft access database and are now being analysed.

Results: 7504 (4220 male, 3284 female) patients were admitted on 8692 occasions. Mean age was 62 (male 58, female 66), 58% were over 60 years. 74% came directly from general practice, 10% from A&E, 7% intrahospital transfers and 9% tertiary referrals. 7029 (81%) had confirmed GI bleeding: 5101 (59%) upper GI bleeding (UGIB); 1244 (14%) colonic bleeding (CB); 23 (0.25%) small bowel bleeding; and 661 (8%) source not found. Of the 4186 with haemodynamic compromise, 3425 (82%) had confirmed GI bleeding: 2574 (61%) UGIB; 525 (12%) CB; 15 (0.36%) small bowel bleeding; and 313 (8%) no source found. 3099 admissions required blood transfusion, of whom 2211 (71%) had UGIB, 408 (13%) had CB, 246 (8%) source not found, 19 0.6%) small bowel bleeding, and 143 (5%) had no evidence of acute GI bleeding. Patients requiring transfusion received an average of 3.5 units and a total of 10 974 units of blood were given over 10 years. Referral rates did not change, but the proportion of patients over 70 increased. There was a relative increase in the number of colonic bleeds, with a decrease in the number of UGI bleeds, although the case mix was similar.

297 SURGICAL MANAGEMENT OF ACUTE NON-VARICEAL GASTROINTESTINAL BLEEDING: A PRE-MORTAL EVENT

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Introduction: A small group of patients require urgent life saving surgery for upper gastrointestinal bleeding. Fewer surgeons are experienced in operating for peptic ulcer disease and the patients are usually elderly and at high surgical risk. The recent trend is to perform less radical and quicker surgery by undersewing rather than a definitive procedure. The aim of this study was to analyse the results of surgery and to see whether a less radical operation affected mortality in one hospital.

Methods: All patients with acute upper gastrointestinal bleeding between June 1998 and June 2002 were entered onto a prospectively maintained database. Those undergoing emergency surgery were identified and their notes reviewed to assess surgical intervention and outcome.

Results: During this period 679 patients had a diagnosis of non-variceal upper gastrointestinal bleeding. Only 24 (3.5%) needed emergency surgery. Their median age was 76 (range 31–90) years and all had significant comorbidity. 19 patients had undersewing of the bleeding lesion, 4 had a partial gastrectomy, and 1 young male had vagotomy only. Consultants were present at 83% of the procedures. Of the undersewing cases, 6/19 (32%) had recurrent bleeding and needed re-laparotomy; none survived. Of all 24 patients having surgery, 19 died and only 5 were discharged from hospital.

Discussion: The mortality in our study for the small number requiring emergency surgery is very high at 79%. This is not surprising because the cohort that fails endoscopic intervention for bleeding is usually old, has significant comorbidities, and many of the cohort had been hypotensive. Most patients had undersewing of the bleeding diathesis, but nearly one third of them had to return to theatre for further haemostasis, resulting in 100% mortality. This study shows that even though a less radical surgical procedure is often performed, survival rates remain dismal for this life threatening event.

298 CLINICAL EFFECTIVENESS OF IV OMEPRAZOLE IN ENDOSCOPICALLY TREATED PEPTIC ULCER DISEASE

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Introduction: Recent RCT data have demonstrated significant benefits of a 72 hour IV omeprazole infusion, for patients undergoing endoscopic haemostasis for bleeding peptic ulcers. This treatment was incorporated into our clinical practice in December 2001

Aims and Methods: To assess the effectiveness of IV omeprazole on outcomes, a retrospective audit of all patients receiving this therapy was audited. This group was compared to all those who received endoscopic therapy (adrenaline injection) alone. Patients were identified from the OGD reports held on database. Case notes were then examined to assess age, Rockall score, time to OGD, blood transfused, rebleeding, surgery, and 30 day mortality. The results were analysed by χ^2 test.

Results: There was 100% case note retrieval. Over 15 months 56 patients (39 DU & 17 GU) received IV omeprazole for 72 hrs after endoscopic haemostasis for bleeding peptic ulcers. 25 controls (14 DU &

11 GU) over the previous 8 months were identified. The median age was (75 *v* 71 years), Rockall score (5.3 *v* 5.1), OGD within 24 hrs (76 *v* 78%), and blood transfused (5 *v* 6.4) units respectively.

Conclusions: Patients receiving IV omeprazole had lower rates of rebleeding, surgical intervention, and mortality. The transfusion requirements and hospital stay were significantly reduced. The controls used were historical and there was no difference in age, risk stratification, and comorbidity. The improvement seen is likely to be a direct effect of omeprazole. The use of IV omeprazole following endoscopic haemostasis is an effective method.

Abstract 298

	Rebleeding*	Surgery	30 day mortality*	Duration of stay
IV omeprazole (n=56)	14.3%	10.7%	8.9%	12 days
Control (n=25)	24%	20%	20%	16.5 days

*p<0.01.

299 THE CLINICAL OUTCOMES AND COST EFFECTIVENESS OF GASTRODUODENAL STENTING IN MALIGNANT DISEASE COMPARED WITH CONVENTIONAL TREATMENT

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Introduction: Expanding metal gastroduodenal stents are now being used more commonly to palliate patients with inoperable malignant gastroduodenal obstruction. Surgical bypass has reported success rate in the region of 90%; however it carries a relatively high complication rate of 25–35% and a peri-operative mortality of up to 2%. In conjunction with higher cost and a prolonged hospital stay this method of treatment is not always appropriate, particularly in patients in a poor state of health.

Aim: Palliation of symptoms and relief of obstruction, so that feeding can continue satisfactorily is the main aim in these patients.

Methods: We reviewed 58 patients with malignant gastric outlet obstruction with a diagnosis of inoperable upper GI carcinoma. The patients fitted into one of 2 treatment groups either receiving conventional surgical treatment or receiving metal stents. A retrospective review was undertaken to obtain data from patient casenotes.

Results: See table.

Abstract 299

	Conventional	Stent
Number of patients	29	29
Positive clinical outcome (able to retain food without vomiting)	17 (58%)	20 (68%)
Mean survival (days)	134 (1 patient still living)	82 (2 patients still living)
Mean cost per patient including readmissions	£9284	£4651

Discussion: This study shows that metal stenting leads to shorter hospital stays, excellent palliation of symptoms, and is markedly cheaper than than the surgical option. The reduced mean survival in the stented group may reflect patient selection bias for this new procedure.

300 EFFECT OF NITRIC OXIDE GENERATED IN THE LUMEN AT GASTROESOPHAGEAL JUNCTION ON THE ADJACENT DIGESTIVE TISSUE IN RATS

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Background: In humans, it has been revealed that luminal generation of nitric oxide from dietary nitrate via salivary nitrite is maximal at the gastroesophageal junction (GEJ) and that its concentration could reach as high as 50 μM (*Gastroenterology* 2002). The high concentrations of nitric oxide thus generated may contribute to the high incidence of neoplasia at GEJ.

Aim: To determine whether high concentrations of nitric oxide generated at GEJ could cause a nitrosative stress on adjacent digestive tissue in rats.

Methods: SD male rats were laid supine on a board with their heads elevated. Micro catheter was placed orally in the stomach and was used for administration of ascorbic acid with pH 2.0 HCl. Another metallic tube was placed orally in the oesophagus and was used for continuous administration of nitrite and thiocyanate (or water alone as a control). In this model, the nitrite administered into the oesophagus was acidified on entering the GEJ and it is reduced to nitric oxide promptly at that site by the reaction with the ascorbic acid pooled in the stomach. Luminal concentration of nitric oxide was measured with an electrode. Concentrations of mucosal glutathione were measured by a colorimetric assay as a marker for tissue damage by nitrosative stress.

Results: After nitrite administration, luminal concentration of nitric oxide at GEJ was 20 μM on average, whereas it was not detected in the distal stomach. The concentrations of mucosal glutathione in gastric cardia were significantly lower in nitrite administered rats compared to control rats, whereas those in distal stomach was similar between both rat groups.

Conclusion: Nitric oxide generated in the lumen at GEJ caused localised consumption of glutathione in the adjacent tissue. This nitrosative stress may contribute to high incidence of neoplasia at that site.

301 THE ROLE OF PROSTAGLANDIN E_2 IN THE ULCER PREVENTING ABILITY OF LEPTIN

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Background: Leptin, the *ob gene* product, is a peptide produced by the adipocytes and is released into the circulation and transported across the blood-brain barrier into the hypothalamus where it regulates energy homeostasis. It has also been found in the stomach where its function is not clear.

Objectives: The primary aim of the study was to investigate the effects of leptin (1–20 μg/kg) on acidified ethanol (AE) and indomethacin induced gastric lesions in the rat and compare it with ranitidine, lansoprazole, and omeprazole and secondly to determine whether prostaglandins E_2 (PGE_2) are involved in their actions.

Methods: Gastric ulcers were produced in rats with AE and indomethacin. The total length of the haemorrhagic lesions, which were approximately 1 mm in width were taken as the ulcer index. Radioimmunoassay was used to determine the concentration of PGE_2.

Results: Leptin (10 μg/kg), lansoprazole (10 mg/kg), and omeprazole (10 μg/kg) showed significant ($p<0.001$) prevention of AE induced ulcer than placebo treated rats. Leptin increased the PGE_2 concentration dose dependently.

Conclusion: Leptin inhibited gastric ulcer formation induced by AE and indomethacin. The ulcer preventing ability of leptin involves activation of the cyclooxygenase and/or nitric oxide (NO) pathways.

This research was supported by a grant from The Faculty of Medicine and Health Sciences, UAE University and Leptin was provided by Amgen Inc, USA.

302 LINEAR EROSIONS OF HIATUS HERNIA AND COLUMNAR LINED OESOPHAGUS ARE RARELY FOUND TOGETHER: IMPLICATIONS FOR THE PATHOGENESIS OF CAMERON'S LESIONS OF HIATUS HERNIA

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Introduction: Linear erosions of hiatus hernia (Cameron's lesions) are believed to be caused by mucosal folds rubbing together in the neck of the hiatus and are associated with iron deficiency anaemia[1]. We have reviewed our endoscopic records for 1996–2000 to identify other associations.

Patients: Forty one patients were identified with a mean age of 71 years (range 50–90, 64% female) of whom 17 (44%) were anaemic. Ulcerated or bleeding lesions were found in 10 (24%) with 42% of the lesions being within the hernia rather than at the level of the hiatus. Seven patients were taking NSAIDs, three PPIs, and one an H_2RA.

Results: Although in 27 (66%) there was endoscopic evidence of reflux, only 6 patients had columnar lined oesophagus (CLO). A further search was therefore undertaken to establish the prevalence of linear erosions in patients with CLO diagnosed 1996–2001. 212 patients with CLO were identified with an average age of 66 years and a prevalence of the two lesions occurring together of 2.8%.

Conclusions: As more than a third of patients with large hiatus hernias have linear erosions[1] and almost all patients with CLO have a significant hiatus hernia,[2] the unexpected low prevalence of the two lesions occurring together raises the possibility that the profoundly incompetent lower oesophageal sphincter which predisposes to CLO also protects against the development of linear erosions.

1. Cameron AJ, Higgins JA. *Gastroenterology* 1986;**91**:338–42.
2. Cameron AJ. *Am J Gastroenterol* 1999;**94**:2054–9.

303 TESTING FOR AND ERADICATION OF *H PYLORI* INFECTION IS INADEQUATELY PERFORMED IN PATIENTS WITH PEPTIC ULCER PERFORATION

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Background: *Helicobacter pylori* (HP) is a major cause of peptic ulcer disease (PUD) and acute duodenal ulcer perforation is one of the commonest complications of PUD. Eradication of HP prevents ulcer recurrence and complications in patients with HP associated perforated duodenal ulcer.

Aim: To review the testing for, treatment of, and reassessment of HP infection in patients presenting with acute perforation from PUD.

Methods: Retrospective case studies with prospective follow up. The case records of all patients presenting with acute perforation from PUD from August 1995 to November 1999 were reviewed. Variables such as previous history of PUD, NASID use, HP status before presentation, pre and postoperative HP status, HP eradication and post eradication reassessment, and outcome were recorded. All the cases were followed up in the community.

Results: Seventy three cases with age range from 18–79 (mean 52) years (41 male:32 female) were identified. All the cases after operation were followed up with a period ranging from 1–64 (median 24) months. History of previous HP eradication were found only in 2 (2.7%) cases. Aspirin and other NASID use were found in 7 (9.5%) and 10 (13.6%) cases respectively. Three (4.1%) patients were on both aspirin and an NASID before presentation. Sixty six (90.4%) perforations occurred in the duodenum, 5 (6.8%) in the antrum or pre-pyloric region, and 2 (2.7%) in the body of the stomach. Preoperative or postoperative HP status checked in only 6 (8.2%) cases. Fifty four cases (73.9%) received HP eradication treatment. There was significant difference between a GI surgeon and a general surgeon in prescribing HP eradication treatment (83% *v* 59% $p<0.03$). Reassessment of HP status after eradication treatment was carried out only in 10 (13.6%) cases. Twelve (16.4%) cases (9 over age of 50 years) died.

Conclusion: HP status was inadequately assessed during and after operation in patients presenting with a perforated PUD. GI surgeons were more likely to prescribe empirically eradication treatment compared with general surgeons. HP status after eradication was rarely established. This practice may have significant impact on ulcer recurrence and complications in patients with HP associated perforated PUD.

304 AUDIT OF SECOND LINE *H PYLORI* ERADICATION IN A DISTRICT HOSPITAL OVER FIVE YEARS

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Introduction: Successful helicobacter eradication is important in the management of patients with peptic ulcer disease. In most patients *H pylori* (HP) is eradicated with the first course of treatment, but there are limited data on the efficacy of second line treatment.

Methods and Aims: We audited our experience of patients treated with a second course of HP eradication over the past 5 years. Patients were tested by C^{13} urea breath test which was performed after 3 months and the results recorded prospectively on a database.

Results: 157 patients received a second course of treatment with quadruple therapy. All received a one week course of lansoprazole 30 mg BD, amoxycillin 500 mg QDS, and DeNol 120 mg QDS. The dose of tetracycline in the regime had been increased from 250 mg to 500 mg QDS part way through the study period. 50 patients had received 250 mg QDS and 107 had the regime containing 500 mg QDS. There was no significant difference between the efficacies of the two regimes, despite the introduction of the higher dose of tetracycline.

Discussion: These results show that second line therapy with quadruple therapy is effective in approximately half of patients treated. The increased dose of tetracycline did not result in an increase in efficacy. There is still a need for improvements in the treatment regimes for HP and the optimal second line therapy has yet to be established.

Abstract 304

	250 mg tetracycline	500 mg tetracycline	Overall
Number of patients	50	107	157
Number breath test negative	28	49	77
% HP eradication	56%	46%	49%

305 EEFECT OF *H PYLORI* ON QUALITY OF LIFE IN PATIENTS ON LONG TERM PROTON PUMP INHIBITOR THERAPY IN PRIMARY CARE

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Background: Despite the significant impact on NHS resources due to long term PPI prescribing in primary care, little research exists concerning quality of life (QOL) in these patients.

Objectives: To ascertain the QOL in patients on long term PPI therapy and determine any differences between *H pylori* positive and negative patients.

Methods: A long term prescription was defined as a repeat prescription for PPIs which had been started at least 6 months previously and was obtainable by the patient without a further consultation with the general practitioner—that is, on a ''repeat'' basis.

Consenting and eligible patients from eight computerised general practices were invited to have the C^{13}UBT in their local surgery. Before the test, all patients completed three standardised questionnaires; Leeds dyspepsia (LDQ), Carlsson-Dent (CD), and EQ-5D (EuroQol). The data were entered into excel spreadsheet for analysis.

Results: Of the 106 patients (63 F, 43 M, mean age 64.8) undergoing the UBT, 20 (19%) were positive for *H pylori*. All patients (100%) reported dyspepsia symptoms in the last four weeks on the LDQ. The mean dyspepsia score was 15 (5 to 28) and there was no difference between *H pylori* positive, 14 (5 to 26) and negative, 16 (7 to 28), $p>0.05$. On the CD questionnaire, the mean score was 5.8 (0 to 15) and there was a trend towards a higher score in the *H pylori* negative patients (7 *v* 5, $p=0.06$). The mean score of patients' self assessment of their health state on the visual analogue scale of the EQ-5D was 58.0 (35 to 80). For *H pylori* positive, the mean score was 72.0 and for the negative group, 44.0.

Conclusions: *H pylori* does not influence dyspepsia symptoms in patients on long term PPIs. However, reflux symptoms appear to be more severe in the *H pylori* negative patients who also rated their overall health much worse compared with the positives.

306 *HELICOBACTER FELIS* INDUCES HYPERGASTRINAEMIA, ECL CELL HYPERPLASIA, AND GASTRIC CARCINOIDS IN MONGOLIAN GERBILS

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Introduction: Short term studies have shown that *H felis* infects the Mongolian gerbil causing gastritis, but the pathological effects of long term *H felis* infection in gerbils are unknown.

Aims: To evaluate pathology induced by *H felis* in the gerbil and to compare the effects of *H felis* and *H pylori* SS1 strain in this model.

Methods: Male gerbils were orally challenged with *H felis* (HF) or *H pylori* (HP) SS1 strain. Infected animals ($n=33$) plus controls ($n=17$) were sacrificed at 36 and 62 weeks post-infection (PI). Infection was confirmed by culture and/or histology. Serum gastrin was measured by

radioimmunoassay. Haematoxylin and eosin, and anti-chromogranin stained sections were used to grade gastric pathology and enterochromaffin like (ECL) cells respectively.

Results: All HF and HP inoculated gerbils were infected. Gastric pathology with HF at 62 weeks PI was greater in the corpus than the antrum, consisting of marked atrophy of parietal/chief cells, cystic changes and mucous metaplasia. In the antrum at 62 weeks, HP was associated with significantly greater chronic inflammation ($p<0.05$), polymorph activity ($p<0.005$), and atrophy ($p<0.003$) than HF. In the corpus no significant differences in chronic inflammation and atrophy were observed, but HF was associated with significantly greater activity ($p<0.05$) and ECL cell hyperplasia ($p<0.01$) than HP. At 62 weeks PI serum gastrin was significantly increased in HF (109 (SD 57.2) pM, $p<0.001$) but not HP infection (42.3 (SD 13.6); $p=0.09$) compared with uninfected controls (10.3 (SD 1.8)). Gastric carcinoids were present in 3/15 HF infected gerbils but absent in 18 HP SS1 strain infected gerbils.

Conclusions: Gastric pathology induced by HP SS1 strain and HF in the gerbil differs. Long term HF infection results in corpus predominant gastritis, elevated gastrin, ECL cell hyperplasia, and gastric carcinoids.

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307 DOES MICROBUBBLE ULTRASOUND HELP WITH HEPATOCELLULAR CARCINOMA SCREENING IN PATIENTS WITH HCV RELATED LIVER DISEASE?

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Purpose: Microbubble ultrasound has been shown to improve detection of focal liver lesions particularly in metastatic disease. The aim of this study was to investigate the use of microbubble ultrasound as a screening test for patients with hepatitis C virus (HCV) related liver disease who have a 3% per annum risk of developing hepatocellular carcinoma (HCC).

Materials and Method: 100 (62 M:38 F) patients with biopsy proven HCV induced liver disease (HCV RNA positive PCR) were recruited. Initial grayscale and Doppler ultrasound scans were performed by an experienced sonographer (NP). Levovist 4 g (Schering AG, Berlin, Germany) was injected and sweeps were made through the liver after 4 minutes using the ADI mode (Agent Detection Imaging, Sequoia, Siemens). Scans were repeated at 6 months and 1 year.

Results: There were 20 patients with mild hepatitis, 43 with moderate/severe hepatitis and 37 with cirrhosis (Ishak histological scoring). To date, 44 patients have attended for the 6 month follow up scan and 27 have had scans at 1 year. No focal lesions were detected in any patient on the initial scan. Two patients with cirrhosis were found to have HCC, one at six months and the other at one year. The lesions (2 and 3 cm respectively) were both seen on fundamental scanning. The addition of Levovist confirmed characteristics documented for carcinoma, but did not allow detection of additional lesions.

Conclusion: This study suggests that ultrasound using a microbubble agent does not improve detection of hepatocellular carcinomas in a high risk population and therefore confers no benefit as a screening tool.

308 RELATIVE ACCURACY OF RADIOLOGISTS' EXPERIENCE AND PROGRESSIVE COMPUTED TOMOGRAPHIC SYSTEM TECHNOLOGY IN THE STAGING OF OESOPHAGEAL CANCER

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Background: Computed tomography (CT) system technology has advanced significantly over the last decade. Moreover, variations in the interpretation of oesophagogastric cancer stage exist, even between experienced radiologists.

Aims: The aim of this study was to measure the serial accuracy of the perceived preoperative stage of oesophageal cancer with respect to radiologists' experience and progressive CT system technology.

Methods: Seventy six consecutive patients (median age 61 years, 52 male) with oesophageal carcinoma (59 ACA, 17 SCC) underwent a preoperative CT performed by our MDT specialist radiologist followed by surgery within 10 weeks (22 patients received neoadjuvant chemotherapy). The CT systems used were upgraded from a General Electric 9800 incremental CT (iCT) to a Siemens Somatom +4A helical CT (hCT) in 1997 and to a Toshiba Aquilon multislice helical CT (mCT) in 2002. The strength of the agreement between the perceived CT stage and the histopathological stage was determined by means of the weighted Kappa statistic.

Conclusion: Increasing experience and improved technology resulted in a 50% improvement in the perceived preoperative T stage and a 75% improvement in N stage. The role of CT in staging oesophageal cancer is becoming stronger as CT technology improves.

Abstract 308

Results	Weighted Kappa statistic				
Series number		1–10	11–35	36–60	61–76
Number cases	10	25	25	16	
Scanner	iCT	hCT	hCT	mCT	
T stage		0.42*	0.62	0.63	0.77
N stage	0.62	0.61	0.59	0.82	

*$p=0.07$, (all other p values <0.05)

309 EXPERIENCE WITH A LAPTOP BASED 3D DICOM READER AT MDT MEETINGS IN A DISTRICT GENERAL HOSPITAL

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Background: Multidisciplinary team (MDT) cancer meetings are frequently too large to be held in radiology departments, although much of the discussion at MDT meetings revolves around the radiologist's interpretation of the patient's imaging. Our hospital, like many district general hospitals (DGHs) in the UK, does not have a full PACS system so the radiologist has to show the films either on a viewing box or via an OHP.

Aim: To modify a PC based 3D volume rendering application developed by two of us (RSR and RL) for research purposes into a more user friendly application for presenting good quality radiological images, extracted from DICOM files, via a data projector at our weekly MDT meetings.

Methods and Results: DICOM files from a selection of patients who had undergone high resolution multidetector row CT scans were burned to CD using the existing CT workstation facilities. The new software runs on a modern laptop computer with a powerful graphics card (128MB Nvidia GeForce FX), and accesses data directly from these CDs. The quality of the images and their refresh rate was judged to be as fast as the hospital's SG Workstations. The visualisation options include 3D volume view, axial, coronal and sagittal views, maximum intensity projection (MIP), multi-planar reformatting (MPR), and moveable cut planes. Other features include interactive window/level and transfer function, and the ability to save images to bitmap format. Ease of use is an important consideration in the MDT setting and the software has been designed so that all of these features are selected using simple menus. Clinicians and particularly their trainees attending the MDT meetings at which the patients' radiological images were projected up onto a large screen seem to appreciate their clarity and the ability to both see and think in 3D with the aid of the MPR facility.

Conclusions: We have shown (1) that with our software and a suitable laptop computer costing about £2K it is possible to reproduce virtually all of the common functions that can be currently found on a SG Workstation costing 6–10 times as much and (2) linking such a system to a data projector is a relatively inexpensive way of showing radiological images at large MDT meetings.

310 USE OF SELF EXPANDING METAL STENTS FOR PALLIATION OF INOPERABLE GASTRIC CANCER

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Introduction: Self expanding metal stents (SEMS) have been successfully used in the management of oesophageal cancers. However there have been few data that have demonstrated successful deployment of gastric stents for palliation of gastric cancers.

Aims and Methods: The aim of this study was to assess the safety, efficacy, and success of SEMS in the management of inoperable stomach cancer. We reviewed 11 patients with inoperable gastric cancer who underwent 15 stent placements over a four year period. All but one

patient had stent placement under fluoroscopic control. One was put under endoscopic guidance. All patients were followed up for a mean of 12 weeks. All complications and hospital stay were recorded. End points included relief of symptoms and improved quality of life.

Results: Technical success was seen in all patients (100%). Three patients (27%) had problems with tumour ingrowth which was successfully treated with restenting/ballon dilatation. Slight stent migration was seen in two (18%) patients which were successfully restented. Nine patients (82%) had substantial improvement in quality of life with restoration of normal diet and relief of symptoms. Average hospital stay post stent was four days. Nine patients (82%) died due to non-stent related complications. Two (18%) patients died 8–14 days after stent placement.

Conclusion: We have shown successful palliation with SEMS. None of our patients required any surgery and no complications were seen. Moreover due to improved symptoms, hospital stay was reduced. However, due to problems with migration there is a need to develop a stent which is stable in the gastric anatomy. We hope this study would encourage widespread use of expanding metal stents for palliation of inoperable gastric cancer.

311 SMALL BOWEL BARIUM STUDY SHOULD BE AVOIDED AFTER A NORMAL ILEOSCOPY AND TERMINAL ILEUM BIOPSY AND AN UNREMARKABLE COLONOSCOPY

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Background: Small bowel barium study (SBBS) is the standard way of imaging the small intestine in order to exclude or establish the diagnosis of Crohn's enteritis. However, the yield is generally low and the radiation exposure not insignificant. Furthermore, the most frequent site of inflammation in such patients, the terminal ileum, can be assessed in details during ileoscopy at colonoscopy.

Aim: The aim of this study was to evaluate the diagnostic yield of SBBS in patients who have had a normal ileoscopy and an unremarkable colonoscopy.

Methods: 96 patients who had a normal ileoscopy and an unremarkable colonoscopy (82 normal, 7 diverticular disease, 5 polyps, and 2 diverticular disease and polyps) followed by a SBBS were identified. Patients with an established diagnosis of inflammatory bowel disease prior to the colonoscopy were excluded. The indications for the colonoscopy were as follows: change in bowel habit 40; abdominal pain 25; anaemia 10; low serum B12 8; rectal bleed 8; abnormal CT 2; abnormal barium enema 1; buccal pigmentation 1, and granuloma on rectal biopsy 1. The results of the SBBS were analysed.

Results: Out of the 96 patients, only 3 had abnormalities detected at SBBS. One patient had a normal ileoscopy but the terminal ileal biopsy revealed a granuloma and the SBBS revealed 3 strictures in ileum. The terminal ileal biopsy of the second patient showed focal cryptitis and the SBBS showed ileal stricture and ulceration. The ileum was also macroscopically normal. The barium study of the third patient found a dilated duodenum and jejunum consistent with the previously established diagnosis of systemic sclerosis.

Conclusion: This study suggests that small bowel barium study does not appear to add any additional diagnostic information in those patients who have had a normal ileoscopy, an unremarkable colonoscopy as well as a normal terminal ileal biopsy and should generally be avoided. In those with suspected Crohn's disease, it is important to take terminal ileal biopsies even if the ileum appears macroscopically normal at ileoscopy.

312 ASSESSMENT OF BOWEL PREPARATION EFFICACY USING ORAL BARIUM IN ''PREPLESS'' CT VIRTUAL COLONOSCOPY

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Aim: To establish if oral barium used for faecal tagging in ''prepless'' CT virtual colonoscopy (CTVC) is effective and gives reproducible results.

Methods: Ten patients under investigation for iron deficiency anaemia were assessed in a study comparing ''prepless'' CTVC using oral barium with conventional endoscopic colonoscopy. Barium in the form of four doses of Readi/cat-2 (EZEM) smoothies was given to each patient. The first dose was given on the evening 2 days prior to the CTVC, the second, third, and fourth doses on the morning, afternoon, and evening respectively of the day before the CTVC. CTVC was performed with a PHILIPS MX-8000 scanner, with slice columation of 2 mm, and prone and supine acquisitions were obtained, after administration of intravenous buscopan and rectal insuflation with room air. Analysis of multiplanar reformatted images were performed on a workstation. Four areas of the colon (ascending (ASC), transverse (TRA), descending (DES), and rectosigmoid (RS)) were studied by two independent readers, and the area of tagged stool was measured. To assess the evenness of tagged stool distribution, the ratio of area of tagged stool in the ascending and rectosigmoid colon (ASC:RS) was calculated for each patient by each reader. The readers' results were compared using Spearman's rho, *r*.

Results: No areas of non-tagged stool were identified in this group. The table shows means of tagged stool areas for each colonic area, ASC:RS ratio and correlation coefficient (*r*) between readers.

Conclusion: Measurement of the efficacy of the stool tagging agent is reproducible. This will allow comparison of bowel preparation and the future refinement of bowel preparation regime and dosage.

Abstract 312

n = 10	ASC	TRA	DES	RS	ASC:RS
Reader 1	1386	2169	834	458	577
Reader 2	1389	2167	834	460	578
Correlation	$r = 1.0$, $p = 0.01$	$r = 1.0$, $p = 0.01$	$r = 1.0$, $p = 0.01$	$r = 1.0$, $p = 0.01$	$r = 1.0$, $p = 0.01$

313 IMPACT OF MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY ON ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

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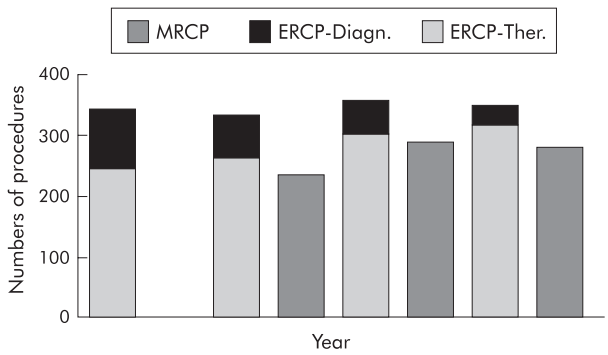
Background: Magnetic resonance cholangiopancreatography (MRCP) provides accurate depiction of the biliary tree without the associated risks of endoscopic retrograde cholangiopancreatography (ERCP). There has been no evaluation, to date, of the clinical impact of this new modality.

Aim: To determine whether the availability of MRCP in our institution in 2000 has had an impact on the ERCP service.

Method: We reviewed 1403 consecutive ERCPs between 1999 and 2002 to evaluate the number of diagnostic versus therapeutic procedures during each successive year. For the years 2000–2002, we evaluated the number of patients undergoing only MRCP and those having both procedures. Finally we compared the indications for ERCP and MRCP.

Results: In 1999, before the availability of MRCP, 347 ERCPs were performed on 168 males and 179 females, mean age 62.4 (SD 16.8) years (median 65 years). 33% were diagnostic. In 2000, 333 ERCPs were performed and 23.4% were diagnostic. In the same year 234 MRCPs were performed and 95 patients (40.5%) also had an ERCP. In 2001, there were 357 ERCPs of which 18.2% were diagnostic. There were 287 MRCPs, with 90 patients (31.3%) also having an ERCP. 70 patients (25%) had a therapeutic ERCP after MRCP. In 2002, 366 ERCPs were performed: 43 diagnostic (13%) and 290 therapeutic ERCPs. 280 MRCPs were also performed.



Abstract 313

Conclusion: There has been a significant decrease in the number of diagnostic ERCPs following the advent of MRCP. The number of therapeutic procedures has increased as has the total number of biliary investigations (ERCP+MRCP), partly reflecting the need to acquire experience with the new modality, but also suggesting that a new, less invasive imaging technique, is ordered more frequently and as a consequence reveals more pathology.

Liver posters 314–367

314 ANONYMOUS STUDY OF HEPATITIS C VIRUS (HCV) PREVALENCE IN LIVER TRANSPLANT SURGEONS

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Background: The risk of HCV transmission from patients to surgeons is related to the prevalence of HCV in the surgical patient population. As HCV related cirrhosis is the commonest indication for liver transplantation in Europe and North America, liver transplant surgeons would be expected to be at particular risk. The prevalence of HCV infection in liver transplant surgeons is unknown.

Aims: To estimate the prevalence of HCV infection in liver transplant surgeons attending the 9th Congress of the International Liver Transplantation Society (ILTS) in Barcelona, Spain, in June 2003 using unlinked anonymous testing for HCV.

Methods: Surgeons attending the conference were asked to complete an anonymised questionnaire regarding their surgical and transplant practice and provide an unlinked anonymised blood spot sample by finger prick. Samples were transferred to the SVC in Glasgow and screened for antibodies to HCV (ELISA III, Ortho Diagnostics, USA). PCR testing for HCV RNA was performed on reactive samples.

Results: 117 liver transplant surgeons (79 European, 16 North American, 10 Asian, 9 South American, 3 Australasian) participated. The reported prevalence of HCV (%, median (range)) in the transplant recipient population of each surgeon was 31 to 40% (1 to >60%). The median (range) number of liver transplants performed by each surgeon per annum was 21 to 30 (1 to >60). Two (1.7%) surgeons had antibodies to HCV, 1 (0.8%) had detectable HCV RNA (genotype 1a). Assuming that both infections were acquired during surgery, the estimated rate of HCV transmission to liver transplant surgeons is 1 per 743 to 1045 years of surgical and 449 to 683 years of liver transplant practice.

Conclusions: The risk of HCV transmission to liver transplant surgeons is reassuringly low despite the particular risks associated with frequently operating on HCV infected patients.

315 COGNITIVE DYSFUNCTION IN PATIENTS WITH HEPATITIS C VIRUS INFECTION AND BIOPSY PROVEN MINIMAL LIVER DISEASE

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Introduction: Over 170 million people worldwide are infected with the hepatitis C virus (HCV). We aimed to establish the presence and nature of cognitive deficits in patients with HCV but no significant liver disease.

Method: Twenty consecutive patients with HCV and biopsy proven minimal liver disease were recruited. Patients with other known chronic viral infections, liver disease, neurological disease, psychiatric disease, or other major illness were excluded. Cognitive function was assessed using a battery of neuropsychological tests, including the Mini-mental State Examination (MMSE), the Rey Auditory-Verbal learning test (RAVLT), Trail making tests, the Stroop test, and the Benton Visual Retention test (BVRT). Health related quality of life was assessed using the EuroQol. The Hospital Anxiety and Depression Scale was used to screen for anxiety and depression. Twenty five healthy volunteers were recruited as controls.

Results: There were 13 males and 7 females with a mean age of 37.3 years (range 24–56 years). The median ALT was 46 IU/l (IQR 38–50.5 IU/l, normal range <40 IU/l). Patients scored significantly worse on the RAVLT ($p<0.0001$) and the Stroop test ($p=0.0004$), but there were no differences in the MMSE, BVRT, or trail making tests. There was no difference between the levels of anxiety or depression in the two groups but the HCV group had significantly lower quality of life scores ($p<0.001$).

Discussion: Hepatitis C virus infection causes cognitive dysfunction independent of its effects on the liver. The impairment is different from that found due to liver disease, with memory and frontal lobe functioning being particularly affected, whilst visuospatial functioning and performance on trail making tests are preserved. This deficit is not due to the presence of psychiatric morbidity. Patients with HCV and no significant liver disease also have a worse quality of life than normal controls.

316 SUSTAINED VIROLOGICAL RESPONSE OF PEGYLATED INTERFERON α-2A PLUS RIBAVIRIN IN PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE 4

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Background: Combination treatment with pegylated interferon α plus ribavirin produces significantly higher sustained virological response than treatment with interferon alone in patients with chronic hepatitis C virus (HCV) infection. Duration of treatment should be based on HCV genotype. Patients with genotype 1 should be treated for 48 weeks. Patients with genotype 2 or 3 should be treated for 24 weeks. There is inadequate information on optimal regimens of treatment for patients with other genotypes, like genotype 4.

Objective: To assess the efficacy (sustained virological response) of pegylated interferon α-2a plus ribavirin for the treatment of patients with chronic hepatitis C genotype 4.

Patients and Methods: We assigned 46 patients with chronic hepatitis C genotype 4 to receive 180 μg of pegylated interferon α-2a subcutaneously once per week plus ribavirin 1000–1200 mg/day orally for 24 weeks. Liver biopsy was done for all patients and the degree of hepatic inflammation and fibrosis was scored with Knodell Histologic Activity Index and Metavir system. Clinical and laboratory assessment including aminotransferases were done every 4 weeks during the study (24 weeks), and during the 24 weeks period of follow up. HCV RNA by RT-PCR was detected every 3 months during the study (24 weeks) and during the follow up period. A sustained virological response (SVR), defined as an undetectable level of hepatitis C virus (HCV) RNA at week 48.

Results: In an intention to treat analysis, the end of treatment response (ETR) was 85%. At the end of follow up period (48 weeks), sustained virological response (SVR) was 46.8%.

Conclusions: Combination treatment for 24 weeks of pegylated interferon α-2a plus ribavirin in patients with chronic hepatitis C genotype 4 produces ETR (85%) and SVR (46.8%). Due to the high rate of relapse, treatment for longer duration (48 weeks) should be tried in order to improve the SVR in genotype 4.

317 NATURAL HISTORY OF CHRONIC HEPATITIS C INFECTION: LONG TERM FOLLOW UP OF ASIAN PATIENTS INFECTED IN CHILDHOOD

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Chronic infection with the hepatitis C virus is common. Infection causes slowly progressive liver damage that leads to cirrhosis in 20% of patients after 20 years of infection. To determine the natural history of chronic hepatitis C infection in patients infected for many decades, we studied liver histology in 143 Asian patients infected in early childhood and compared with 239 white people who were infected in adult life. The prevalence of hepatic cirrhosis increased with age in both groups and in elderly Asian patients the majority had cirrhosis. The prevalence of hepatitis C related cirrhosis in Asian patients aged 61–70 years (n = 22) was 68% and was 85% in Asians (n = 33) who were over 70 years old. In whites aged 61–70 (n = 36) 17% had cirrhosis and in those older than 70 (n = 19) 45% had cirrhosis. We compared the rate of fibrosis progression in Asian and white patients who had had a single liver biopsy and studied fibrosis progression in 48 patients who had had repeat liver biopsies (19 were Asian). No difference in the rate of fibrosis progression in the two populations was seen. Multivariable analysis did not identify any unique Asian characteristic that could explain the high prevalence of cirrhosis in elderly Asians. These data indicate that the

prevalence of cirrhosis in patients with chronic hepatitis C rises with increasing duration of infection and lifelong infection with the hepatitis C virus almost invariably leads to cirrhosis.

318 HEPATITIS C, RURAL AREAS HAVE ''ICEBERGS'' TOO

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Introduction: It is only the tip of the hepatitis C (HCV) ''iceberg'' that is seen for assessment; most data come from urban studies. North Cumbria Acute Hospitals NHS Trust (NCAHT) serves a rural community of 320 000; the size of the HCV problem is unknown. NCAHT receives all serology from primary and secondary care.

Aim: To assess the potential burden of HCV in North Cumbria.

Methods: The numbers of HCV serology/PCR requests received, HCV positivity rates in an anonymous survey of intravenous drug users (IVDU), NCAHT admissions data for HCV, and referral rates of HCV cases were determined.

Results: HCV antibody requests per year rose from 314 in 1993 to 4084 in 2002. From a total of 14 211 tests, 849 were positive from 532 cases. PCR requests increased 11 fold from 1995 totalling 302. Eliminating repeat requests in any one year, the number of positives rose from 6 to 48 per year (total 194). Referral of antibody positive cases rose from 6 per year (2000) to 29 mid 2003 with a 22% FTA rate. By August 2003, 48 PCR positive cases were known to our service, 82% had identifiable risk factors (77.5% IVDU, 4.3% transfusion, 18.2% unknown). In 2003 our needle exchange programme identified approximately 2000 IVDU. Anonymous salivary testing of IVDU showed 47% HCV antibody positives, 16% HBsAg positive, less than one third had received HepB vaccination.

Conclusion: This study shows the increasing burden and unmet need of this disease. Increased testing shows awareness of the disease but further education and resources are required, with evidence of inadequate use of PCR and major deficits in referral. The high FTA rate hampers assessment. Traditionally, referral to liver units has been recommended for HCV management but for our patients this could mean travel in excess of 200 miles. These data support the continued development of locally available services to meet the burden of disease. As with urban populations we currently only see the tip of the ''iceberg''.

319 THE SEROPREVALENCE OF VIRAL HEPATITIS IN YEMENI HEALTHCARE WORKERS

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Background: The Republic of Yemen has one of the highest prevalence rates for hepatitis B (HBV) and hepatitis C (HCV) in the Middle East. The seroprevalence of viral hepatitis in healthcare workers (HCWs) has important public health implications.

Aims: To assess the risk factors for the acquisition of viral hepatitis in an unvaccinated HCW cohort from a hyperendemic region.

Methods: HCWs from a large hospital in the capital of the Republic of Yemen were interviewed for demographic and risk factors for the acquisition of HBV and HCV before being tested for serological markers of infection. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBcAb) and hepatitis C antibody (anti-HCV Ab) levels were measured. An intention to treat analysis was carried out and a multivariate logistic regression analysis used to identify independent risk factors for the acquisition of viral hepatitis.

Results: A total of 567 HCWs were interviewed (313 males, 233 females) with a mean age of 29.3 years (range 19–70). Of 543 suitable samples for analysis, 54 (9.9%) tested positive for HBsAg and a total of 174 (32.0%) were positive for anti-HBcAb. Nineteen out of 546 suitable samples (3.5%) tested positive for anti-HCV Ab. Age, male sex, and occupation (HCWs carrying out exposure prone procedures) were found to be independent predictors for the likelihood of detecting either HBsAg or anti-HBcAb positive status by multivariate logistic regression analysis. No independent risk factors for anti-HCV Ab status were identified.

Discussion: The finding that age and occupational exposure to blood products are independent risk factors for the acquisition of HBV supports the adoption of universal HBV immunisation programmes and infection control precautions. The absence of known risk factors predicting anti-HCV Ab positive serostatus suggests the main mode of transmission of HCV in this cohort in the Yemen remains undiscovered.

320 TRANSITION FROM ACUTE TO CHRONIC VIRAL INFECTIONS—A TISSUE CULTURE MODEL USING RESPIRATORY SYNCITIAL VIRUS INFECTED CELLS

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Background: Chronic viral hepatitis with hepatitis B or C is one of the leading causes of hepatic morbidity and mortality. Factors that influence transition from acute to chronic viral infection are not fully understood. We have developed a tissue culture model of chronic viral infection using an RNA virus (respiratory syncitial virus) that infects transformed human B cells. Transformed B cells (10^6 in 10 mls RPMI) were incubated with 2×10^8 viral particles for a total of 14 days leaving the cells undisturbed. Chronic infection was assessed by direct cell staining and by quantitative PCR. After incubation for 14 days, >90% of the cells expressed RSV antigens. Viral RNA was detected in the supernatant. The cells were maintained in culture for 16 weeks and passaged every two weeks (cells split 1:3 and the media exchanged). The cells were treated with interferon 2a (500 IU/ml) to assess the effects of antiviral treatment.

Results: Low titres of viral innoculum in the early phase of infection did not induce chronic infection. Higher titres of virus led to a brief period of cell death followed by recovery of cells that were chronically infected. Mathematical modeling of factors that modify the acute to chronic transition of infected cells by FACS analysis of apoptotic, necrotic, and infected cells is in progress. When treated with IFNα the number of cells expressing RSV declined within 48 hours. Data on the effects of IFNα on RSV titre and cell death and apoptosis are being collected.

Conclusion: This new model of chronic viral infections allows an in vitro analysis of the factors influencing viral persistence and will allow an analysis of the effects of IFNα in the absence of an IFNα induced immune response.

321 A PROSPECTIVE STUDY TO ASSESS RESPONSE TO THREE MONTHS OF COMBINATION TREATMENT IN CHRONIC HEPATITIS C INFECTION

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Background: Clinical trials suggest treating genotype 1 hepatitis C with combination treatment for 12 months and genotype 2/3 for 6 months. However, this prolonged course of treatment reduces compliance and puts enormous strain on budgets, thereby limiting its use.

Patients and Methods: This prospective study recruited 51 patients, following ethics committee approval, of whom 33 (65%) were male and 18 (35%) were female, age range 22–56 years. 44% were genotype 1 and 56% were genotype 2/3. The majority of these patients (80%) had mild to moderate hepatitis as assessed by the Ishak scoring system. Four (8%) had severe hepatitis and 6 (12%) had cirrhosis. They received 3 months of combination treatment, consisting of weekly PEG interferon 1.5 mcg/kg and ribavirin 400 mg twice daily. To improve compliance PEG interferon was given either at the hepatology clinic, or at the GP's surgery. Monthly PCR testing assessed their response to treatment.

Results: A compliance of 96% was achieved. Treatment in two patients had to be temporarily stopped due to severe anaemia. The side effect profile in this study was similar to other major studies. Surprisingly, patients with leucopenia responded well to dose reduction.

At the end of three months treatment 70% of genotype 2/3 and 52% of genotype 1 were hepatitis C PCR negative. Non-responders were treated with a further course of treatment as per NICE guidelines. Twelve months following treatment 50% of genotype 2/3 and 14% of genotype 1 were hepatitis C PCR negative.

Conclusion: This study has shown that 3 months treatment may be adequate for patients with genotype 2/3 hepatitis C; however the higher rate of relapse in genotype 1 may indicate the need for 6–12 months combination therapy.

322 HOST AND VIRAL CHARACTERISTICS ASSOCIATED WITH STEATOSIS IN CHRONIC HEPATITIS C

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Background: Steatosis is a frequent histological finding in chronic hepatitis C; however, the pathophysiology of steatosis and its role in disease progression is controversial. It has been suggested that steatosis is associated with genotype 3 and that steatosis could accelerate progression of fibrosis. However most studies of hepatitis C associated

steatosis have been performed in areas where genotype 1 predominates, and are limited by having small numbers of genotype 3.

Aim: To address this we studied 221 patients with liver biopsy proven chronic HCV, 107 of whom were infected with genotype 3. Age, alcohol consumption, body mass index (BMI), and HCV genotype were correlated with steatosis and fibrosis (liver biopsies assessed by Ishak scoring system[1]).

Results: Steatosis was found in 47% of liver biopsies (54% of patients with genotype 3, 40% of patients with genotype 1). In univariate analysis, steatosis correlated with clinical obesity (BMI $\geq$30) ($p<0.01$), but not with age, alcohol consumption, or HCV genotype. On repeat analysis of patients with BMI <30 (n=192), steatosis was significantly associated with genotype 3 ($p<0.02$). In multivariate analysis BMI $\geq$30 was the only independent predictor of steatosis ($p=0.001$).

No correlation was found between steatosis and severity of HCV liver fibrosis, in agreement with recent data in French patients.[2]

Summary: In this large cohort of patients (including 107 patients with genotype 3 infection) steatosis is strongly associated with the host factor of obesity, rather than alcohol consumption. Genotype 3 infection may influence steatosis in individuals who are not clinically obese. Our data indicate that risk factors for non-alcoholic fatty liver disease need to be addressed in all patients with chronic HCV.

1. Ishak K, Baptista A, Bianchi, *et al. J Hepatol* 1995;**22**:696–9.
2. Asselah T, Boyer N, Guimont MC, *et al. Gut* 2003;**52**:1638–43.

323 OBESITY AND NON-ALCOHOLIC FATTY LIVER DISEASE

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Introduction: The prevalence of obesity is increasing worldwide. In the future, mortality related to obesity is expected to exceed that of smoking. Non-alcoholic fatty liver disease (NAFLD) is one the diseases that are induced by obesity. NAFLD has a spectrum of liver disease, ranging from simple steatosis to steatohepatitis (NASH), advanced fibrosis, and cirrhosis. The aim of this study was to determine the prevalence of NAFLD and its spectrum among obese patients.

Methods: Thirty obese patients (mean of BMI; 45.8 (SD 7.3) kg/m^2) who were candidates for intestinal bypass surgery and 143 obese patients (BMI $\geq$30) who referred to a nutritionist for weight reduction were studied. A liver biopsy was obtained during the surgery of those 30 patients. The degree of steatosis (0–4), necro-inflammation (0–18), and fibrosis (0–6) was scored in the all liver biopsies by a single liver pathologist. A history—from cases and their families—about alcohol and medication consumption, BMI, viral markers, serum ALT levels, and liver ultrasound were taken from those 143 patients. If ALT was elevated (>40 U/l), it was rechecked twice within 6 months. Patients with persistently high ALT levels ($\geq$2 times) with negative test results for viral hepatitis B and C, autoimmune hepatitis screening (γ globulin <1.5 times the upper normal limit), transferrin saturation <45%, no alcohol and medication intake, and evidence of fatty infiltration in their liver sonography were considered as presumed NASH.

Results: Of the liver biopsies 20% (n=6) had normal histology, 43.3% (n=13) had steatosis, and 36.7% (n=11) had NASH. Among those 143 patients, 23.8% (n=34) had normal liver ultrasound and no elevated ALT (normal), 58.0% (n=83) had fatty liver in their ultrasound without elevated ALT (steatosis), and 18.2% (n=26) had presumed NASH.

Conclusion: Prevalence of NASH among obese patients is about 6–10 times more than general population. Pathogenesis other than obesity is necessary to developing NASH.

324 NAFLD: NEED FOR A MORE AGGRESSIVE APPROACH

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Introduction: Non-alcoholic fatty liver disease (NAFLD) is a disease of emerging importance. It is associated with the metabolic syndrome comprising obesity, insulin resistance, hyperlipidaemia, and hypertension. The pathophysiology involves two steps: insulin resistance causing steatosis followed by oxidative stress, which produces lipid peroxidation and activation of inflammatory cytokines resulting in steatohepatitis. NASH (non-alcoholic steatohepatitis) is associated with fibrosis in 15–50% of patients (James, *et al. J Hepatol* 1998).

Aim: To determine prevalence of the components of the metabolic syndrome in our white patient cohort with biopsy proven NASH.

Methods: We carried out a retrospective review of the case notes of 49 (age 30–70, M:F ratio 29:20) patients referred with abnormal LFTs who had biopsy proven NASH. Patients with significant alcohol intake, viral hepatitis, and autoimmune and metabolic liver disease were excluded.

Results: 32/49 (65%) patients were obese with a mean body weight of 92 kg. HbA_1C was recorded in 35 non-diabetic patients and was elevated (mean −6.8%) in 18/35 patients (51%). However 8/35 (23%) of these patients weighed <70 kgs. Cholesterol was measured in 27 patients; it was elevated in 14/27 (52%) patients yet only 5/14 (35%) were on a statin. 11/49 (22%) patients had hypertension, most were poorly controlled.

Conclusion: NASH is usually associated with obesity and impaired glucose metabolism. Weight loss results in improved insulin resistance and liver function. However, in our cohort, nearly a quarter of patients were lean but had evidence of impaired glucose metabolism suggesting that NASH is associated with insulin resistance irrespective of obesity. This cohort may be suitable for targeted intervention with metformin to improve insulin sensitivity. Treatment with statins is often delayed or avoided altogether due to impaired liver function. The risk of progression to cirrhosis coupled with increased cardiovascular risk merits early and aggressive management of hyperlipidaemia.

325 MEDIEVAL THERAPY FOR A MODERN DISEASE? PRELIMINARY RESULTS OF A RANDOMISED CONTROLLED TRIAL

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Background: Non-alcoholic steatohepatitis (NASH) is an increasingly recognised clinical problem with few if any accepted treatments. Hepatic iron may be a cofactor for hepatic fibrosis in NASH.

Aims: To assess the effect of iron depletion by venesection treatment on liver function tests (LFT), liver histology, and patient wellbeing in NASH.

Methods: Patients with a clinicopathological diagnosis of NASH and detectable histological iron staining or hepatic iron concentration >20 μmol/g dry weight were randomised to treatment by attempted weight reduction (group A) or attempted weight reduction and venesection treatment (group B). LFT and patient quality of life data were collected over the 9 month study period. Repeat liver biopsies were performed on consenting patients after 9 months. Liver biopsies were scored by a single pathologist (DF) according to the method of Brunt, blinded to the patients' details.

Results: To date 8 patients have been randomised to each group. Mean weight in group A was 94.1 (SD 16) kg (BMI 31.8 (SD 3.6)) and in group B was 89.1 (SD 13) kg (BMI 29.8 (SD 2.5)). Six patients in group A have completed the 9 month study period, of whom 3 have had repeat liver biopsies. Seven patients in group B have completed the study, all with repeat liver biopsy. In group B, mean AST and ALT levels were significantly reduced within 1 month of starting treatment ($p=0.01$) and at all study points ($p<0.05$), maximal at 5 months (mean AST 0 months 50 (SD 23) U/l *v* 5 months 30 (SD 5) U/l, $p=0.028$; mean ALT 0 months 67.3 (SD 34) U/l *v* 5 months 35.1 (SD 12) U/l, $p=0.013$). In group A neither mean AST nor ALT levels significantly improved at any study point. In group B, 5 of 7 patients showed an improvement in fibrosis score compared with 1of 3 in group A ($\chi^2=1.2$, NS). Mean fibrosis grade in group B improved from 1.43 to 0.57, ($p=0.008$).

Conclusions: Venesection therapy is a promising treatment for a subgroup of NASH patients.

326 INCREASED PREVALENCE OF IgM ANTICARDIOLIPIN ANTIBODIES IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

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Aim: In patients with non-autoimmune liver disease, anticardiolipin antibody (aCL) production is considered to be an epiphenomenon of liver damage not associated with thrombotic complications. There are sparse reports of increased non-specific prevalence of aCL in patients with primary biliary cirrhosis (PBC). We aimed to evaluate the presence of aCL and anti-β 2 glycoprotein antibodies (aβ2-GPI) in a cohort of patients with PBC.

Methods: The presence of aCL and aβ2-GPI was assessed in 50 PBC patients and 100 healthy controls (blood donors). Sera were analysed for IgM and IgG aCL by a cardiolipin-isotypin ELISA (Fresenius Gull Diagnostics). The detection of IgM and IgG aβ2-GPI was performed using a semiquantitative ELISA (Quanta Lite β2 GPI IgM and IgG, Inova Diagnostics). Statistical analysis was performed using *t* test and one way ANOVA test. Statistical significance was set at 0.05.

Results: Mean age of PBC patients was 66.3 yrs (range 45–88). According to Schewer classification of liver histology, 26 PBC patients had stage I–II and 24 patients stage II–IV disease. Antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) were detected in 8 (16%) and 9 (18%) PBC patients respectively. IgM and IgG aCL were detected in 8 (16%) and 2 (4%) PBC patients respectively, and in 1 (1%) and 2 (2%) blood donors sera respectively ($p=0.010$ and $p=0.239$ for comparison of IgM and IgG aCL between PBC patients and healthy controls). None of the PBC patients had simultaneously detectable levels of both IgM and IgG aCL. The presence of IgM aCL was not related to sex ($p=0.963$), advanced disease stage ($p=0.904$), or simultaneous occurrence of ANA ($p=0.0703$) or ASMA ($p=0.154$). IgM aβ2-GPI were detected in one PBC patient (2%). None of the PBC patients or healthy controls had detectable IgG aCL, IgM and IgG aβ2-GPI.

Conclusions: IgM aCL are frequently detected in patients with primary biliary cirrhosis. Their presence is not related to disease stage, sex, or simultaneous occurrence of ANA or ASMA.

327 SURVIVAL FOLLOWING THE DEVELOPMENT OF ASCITES AND/OR OEDEMA IN PRIMARY BILIARY CIRRHOSIS: A STAGE PROGNOSTIC MODEL

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Background: Current prognostic models in primary biliary cirrhosis (PBC) have low precision, partly due to the restricted inclusion criteria for some cohorts used for modelling but also due to the prolonged natural course of the disease. We hypothesised that better precision could be achieved by a staged model, using ascites or peripheral oedema as a new starting point for prediction.

Methods: We used an established database of 289 consecutive patients, followed between 1977 and 1998. Stepwise Cox regression was used to construct a staged model based on 143 patients who first developed ascites (n=111) or peripheral oedema (n=32) at entry or during subsequent follow up. The model was compared with published models using graphical methods and receiver operating characteristics.

Results: Mean time from clinical diagnosis of ascites or peripheral oedema to death was 3.1 years. The equation for the best model of survival at the time of diagnosis of ascites for PBC patients was $r=1.138$ (Log10 (bilirubin (umol/L))) −0.081 (albumin(g/L)) + 0.053 (age at the time of diagnosis of ascites) + 1.010 (history of encephalopathy at the time of diagnosis of ascites). Goodness of fit showed that the survival probability predicted by the Ascites Stage Model fitted the observed data well. The Ascites Stage Model (ROC 0.8324 (SE 0.0348)), predicted better than the Mayo long term model (ROC 0.7833 (SE 0.0397)), the Mayo repeated patient visit model (ROC 0.7779 (SE 0.0399)) and the Royal Free PBC Prognostic model (ROC 0.7785 (SE 0.0396)).

Conclusion: The Ascites Stage Model gives a better survival estimate for PBC patients once they have developed ascites or peripheral oedema, compared with current models, and demonstrates an advantage of staged models in diseases with a prolonged natural history.

328 LONG TERM URSODEOXYCHOLIC ACID TREATMENT FOR PRIMARY BILIARY CIRRHOSIS: A 12 YEAR FOLLOW UP

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Background: Whether ursodeoxycholic acid (UDCA) slows the progression of primary biliary cirrhosis (PBC) is uncertain according to two meta-analyses. However the randomised trials evaluated have only a median of 24 months follow up. Our aim was to evaluate the potential long term effect of UDCA in PBC.

Methods: We evaluated 209 consecutive PBC patients including 69 compliant with UDCA and 140 untreated (mean follow up 5.79 (SD 4.73) and 4.87 (SD 5.21) years respectively) seen between 1989 and 2001, in whom all complications during follow up were documented prospectively. Comparison was made following adjustment for differences in baseline characteristics according to Cox modelling, and the Mayo and Royal Free prognostic models. A sensitivity analysis for low dose 7–12 mg/kg/day (n=25) and standard/high dose UDCA 13–22 mg/kg/day (n=44) was performed.

Results: Bilirubin and alkaline phosphatase concentrations significantly improved with UDCA (at 36 months, $p=0.007$ and 0.018 respectively) and unadjusted Kaplan-Meier analysis showed benefit ($p=0.028$), as 44 (31%) untreated and 15 (22%) UDCA patients died or had liver transplantation. However, adjusted by Cox modelling ($p=0.267$), Mayo model ($p=0.698$), and Royal Free model ($p=0.559$) there was no difference. The standard/high dose UDCA versus untreated group had no differences. There were no differences with respect to the advent of any complications including new pruritus or fatigue, either before or after adjustment for baseline characteristics.

Conclusion: Long term treatment with UDCA did not alter disease progression in PBC patients despite a significant improvement in serum bilirubin and alkaline phosphatase consistent with and similar to those seen in UDCA cohorts in randomised trials.

329 QUALITY OF LIFE IN PATIENTS WITH AUTOIMMUNE HEPATITIS MEASURED WITH THE SF-36 HEALTH STATUS QUESTIONNAIRE

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Background: There are few data on quality of life (QOL) in autoimmune hepatitis (AIH).

Aims: Measurement of QOL in patients with AIH, diagnosed by International Group criteria. Comparison with a large general population sample.

Patients: 99 patients (18 men) with AIH mean age 60 (SD 17) years. Duration of disease was 9 (SD 8) years. 16 had abnormal serum ALT (>150 U/l in 8 patients). 35 patients had cirrhosis on liver biopsy. Seven patients had decompensated liver disease (Child's B). 16 patients were not taking immunosuppressive medication, 10 were taking prednisolone alone, 67 were taking azathioprine (31 with prednisolone, 2 with budesonide) and 6 were taking mycophenolate (4 with prednisolone, 1 with budesonide). 53 patients had comorbidity (significant cardiovascular, respiratory, renal, endocrine, rheumatological, or neurological disease). The control group consisted of 7213 people (3252 men) mean age 68 (SD 16) years from the general population.

Methods: The SF-36 health status questionnaire, consisting of 8 domains, was administered in the outpatient clinic to the AIH group. Response rate was 99%. Administration was via post to the control group with a response rate of 82%.

Results: Patients with AIH had a lower QOL than the control group in 3 domains: vitality (46.1 (SD 23.4) *v* 52.7 (SD 21.6); $p=0.002$, Student's *t* test), general health (51.3 (SD 26.7) *v* 58.1 (SD 24.1); $p=0.005$) and mental health (67.0 (SD 22.8) *v* 71.1 (SD 19.9); $p=0.045$). In the general health domain, QOL was lower in AIH patients with cirrhosis (41.7 (SD 29.0) *v* 56.6 (SD 23.9); $p=0.007$) and in those with comorbidity (44.6 (SD 26.4) *v* 59.1 (SD 25.1); $p=0.007$) than in those without these features. In contrast, QOL showed no correlation with age, gender, ALT, duration of disease, or presence of decompensation.

Conclusions: Patients with AIH have significantly impaired QOL when compared with the general population specifically in terms of their perception of general health and vitality.

330 OSTEOPOROSIS IN CHRONIC LIVER, INFLAMMATORY BOWEL, AND COELIAC DISEASE: APPLYING THE GUIDELINES IN A DISTRICT GENERAL HOSPITAL

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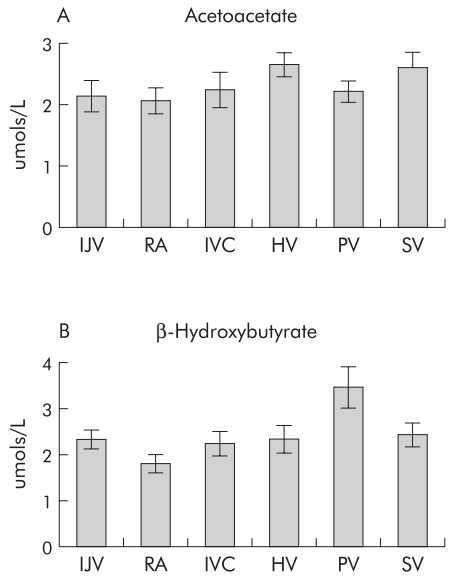
Aim: To audit whether patients with chronic liver disease, inflammatory bowel disease (IBD) and coeliac disease are being investigated and treated for osteoporosis in accordance with BSG guidelines.

Methods: Patients with chronic liver disease at risk of having osteoporosis were identified when attending clinic. Patients at similar risk with IBD or coeliac disease were identified from the relevant databases. Notes were reviewed and audit forms completed comparing investigation and management with recently published BSG guidelines.

Results: The notes of 92 patients with chronic liver disease, 50 with IBD, and 77 with coeliac disease were reviewed. Advice was commonly given with regard to smoking and alcohol, but less often regarding exercise and diet. 9% of liver patients had been DEXA scanned,



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compared with 58% of patients with IBD and 65% of patients with coeliac disease. 67% of patients with liver disease and known osteoporosis were on treatment, compared with 98% of IBD and 100% of coeliac patients.

Conclusions: There was a significant difference in the investigation and treatment of osteoporosis in liver patients and those with IBD and coeliac disease. A larger proportion of IBD patients and coeliac patients underwent DEXA scanning, and when osteoporosis was diagnosed, appropriate treatment was started promptly. The liver patients have a higher concomitant rate of alcohol abuse and may have more complex medical needs than other groups. We feel that the differences in adherence to the guidelines can, at least in part, be explained by the employment of specialist nurses who have set up databases in IBD and coeliac disease. They perform an active role in patient management and help ensure that ''at risk'' patients are identified, investigated, and treated appropriately.

331 KETONE BODIES' METABOLISM IN METABOLICALLY STABLE PATIENTS WITH ADVANCED LIVER DISEASE

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Introduction: Ketone bodies are the end products of fatty acid oxidation and are primarily synthesised by the liver and exported to be used as fuel by other organs. Very little is known about the metabolism of ketone bodies in cirrhosis. We investigated regional variations in the concentration of acetocetate and β-hydroxybutyrate in metabolically stable cirrhotic patients.

Materials and Methods: Sixteen patients were studied. All were Child's B cirrhotics and had normal lactate and glucose levels. At the time of transjugular intrahepatic portosystemic stent shunt (TIPSS) (7 patients) or portographic assessment of the shunt's patency (9 patients) blood was collected from the internal jugular vein, right atrium, intrahepatic inferior vena cava, hepatic vein, portal vein, and splenic vein. Acetoacetate and β-hydroxybutyrate were then measured using nuclear magnetic resonance (NMR) spectroscopy. We used the CPMG sequence for ^{1}H at 600 MHz in an ANOVA Bruker spectrometer.

Results: Acetoacetate results are shown in figure 1A. There was significantly more acetoacetate in the hepatic vein compared with the portal vein ($p<0.04$), the right atrium ($p<0.04$), and the internal jugular vein ($p<0.05$). Results for β-hydroxybutyrate are shown in figure 1B.

There was significantly more β-hydroxybutyrate in the portal vein compared with the internal jugular vein ($p<0.04$), the right atrium ($p<0.005$), the inferior vena cava ($p<0.03$) and the hepatic vein ($p<0.02$). There was also significantly more β-hydroxybutyrate in the splenic vein compared with the right atrium ($p<0.05$).

Conclusions: In cirrhotic patients the liver produced acetoacetate. The brain consumed acetoacetate but not the muscles of the lower limbs. In contrast the liver consumed β- hydroxybutyrate that was produced by the portal drained viscera.

332 BRADYKININ DOES NOT PLAY A ROLE IN THE REGULATION OF PERIPHERAL VASCULAR TONE IN PATIENTS WITH CIRRHOSIS AND ASCITES

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Aims: (1) To establish the role of bradykinin in the maintenance of peripheral vascular tone in cirrhosis; (2) to establish whether patients with cirrhosis have normal endothelial function.

Methods: Eight patients with biopsy proven alcohol induced cirrhosis, ascites, and portal hypertension, and eight age and sex matched healthy controls were recruited. Forearm blood flow (FBF) measurement using venous occlusion plethysmography is a well validated method of assessing peripheral vascular physiology and endothelial function. (1) In the first phase of the study, forearm blood flow was measured during an intrabrachial infusion of B9340, a B1 and B2 receptor antagonist (1.5–13.5 ng/min), followed by noradrenaline (60–540 pmol/min). (2) Subjects re-attended for a second study at least one week later during which they had intrabrachial infusion of the endothelium dependent vasodilator bradykinin at doses (100–900 pmol/min) followed by the endothelium independent vasodilator sodium nitroprusside (SNP) (2–8 μg/min).

Results: Five patients were Child-Pugh grade C and 3 were Child-Pugh grade B; mean age was 54 (SD 2) years, mean bilirubin was 38 (SD 8) umol/l, and mean prothrombin time was 13 (SD 1) seconds. (1) Bradykinin receptor antagonism (B9340) produced no significant effect in either group. In contrast noradrenaline caused a dose dependent vasoconstriction in patients with cirrhosis and controls ($p<0.001$). The vasoconstriction was similar in both groups ($p>0.05$). (2) Both bradykinin and SNP caused a dose dependent vasodilatation in both patients with cirrhosis and controls ($p<0.001$). There were no significant differences in endothelium dependent (bradykinin) or independent (SNP) vasodilatation between the two groups ($p>0.05$).

Conclusions: (1) Bradykinin does not appear to contribute to the maintenance of peripheral vascular tone in patients with cirrhosis and ascites. (2) Patients with cirrhosis do not appear to have marked endothelial dysfunction in the peripheral circulation.

333 THE INFLUENCE OF RENIN-ANGIOTENSIN SYSTEM POLYMORPHISMS ON THE RENAL DYSFUNCTION OF CHRONIC LIVER DISEASE

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Background: Chronic liver disease is associated with renal dysfunction perhaps related to increased activation of the renin-angiotensin system (RAS). Two RAS polymorphisms are the angiotensin converting enzyme (ACE) gene (DD genotype associated with increased activity of ACE) and

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	Child's Grade (A/B/C)	Serum Na	Serum Cr	Urine volume	UNa (mmol/l)	UNa (/24 hrs)	CrCl	RRI
DD and/or TT	1/1/6	134 (4.8)	99 (57)	1550 (909)	62.6 (66.1)	131.4 (88.3)*	83 (39)†	0.706 (0.07)
Others	0/3/4	130 (6.4)	100 (48)	986 (774)	20.4 (24.1)	17.0 (15.3)*	34 (20)†	0.720 (0.05)

Results given as mean (SD). *p=0.025; †p=0.013.

the angiotensinogen (AGT) gene (M235T polymorphism; TT genotype associated with increased angiotensinogen levels).

Aim: Our aim was to investigate whether these polymorphisms were related to renal dysfunction in patients with chronic liver disease.

Methods: We studied 15 patients with chronic liver disease not taking any diuretics. ACE and AGT genotypes were assayed. 24 hour urine samples were collected and renal Doppler studies performed. Creatinine clearance (CrCl), urinary sodium (UNa) and renal resistive indices (RRI) were calculated.

Results: Two patients were DD, four were TT, and two were homozygous for both TT and DD.

Conclusions: Polymorphisms associated with increased RAS expression were not associated with renal dysfunction. On the contrary such polymorphisms may be beneficial with increased natriuresis and improved CrCl.

334 SERUM HYALURONIC ACID AND CONTRAST ENHANCED ULTRASOUND IN THE DIAGNOSIS OF CIRRHOSIS

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Background: We have previously documented the value of contrast enhanced ultrasound in the assessment of the severity of liver disease. No direct comparison between serum markers such as hyaluronic acid (HYA) and ultrasound has been reported.

Aim: To compare hepatic transit times (HTT) with serum HYA in patients with cirrhosis, hepatitis C and normal controls.

Patients and Methods: HTT and serum HYA were measured in 8 subjects with biopsy proven hepatitis C, 14 subjects with proven cirrhosis, and 2 control groups of 17 patients who had serum HYA measured or HTT assessed. HTT were assessed by performing an intercostal scan of the hepatic vein (HV), hepatic artery (HA), and portal vein simultaneously with a bolus injection of 1 ml of Sonovue. The hepatic vein transit time (HVTT) was defined as the time from injection until appearance of contrast (seen with Doppler) in the HV and the ''intrahepatic time index'' (ITI) as the difference between the HV arrival time and the HA arrival time. Serum HYA was assessed with an ELISA test (Corgenix).

Results: See table.

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	Controls	Hepatitis C	Cirrhotics	ANOVA
ITI (secs)	15.3 (3.2)	12.6 (2.3)	7.5 (2.4)	$p<0.0001$
HVTT (secs)	32.8 (5.3)	28.1 (6.1)	18.8 (5.2)	$p<0.0001$
HYA (ng/ml)	46.4 (47.5)	169.8 (185.6)	456 (324.5)	$p<0.0001$

Pairwise comparison between controls and cirrhotics were significant for all variables ($p<0.0001$) and between cirrhotics and hepatitis C patients ($p<0.02$). Pearson correlation between ITI and HYA was $r=0.324$ and between HVTT and HYA $r=0.338$.

Conclusions: Serum HYA, ITI, and HVTT are significantly different between cirrhotics and controls and hepatitis C patients. There is no correlation between HYA and ITI or HVTT, which reflects the overlap between HYA levels in the patient groups studied. In our study the ITI is a more reliable method for predicting cirrhosis.

335 ASSESSMENT OF THE ACUTE HAEMODYNAMIC RESPONSE TO PROPRANOLOL IN PATIENTS WITH CIRRHOSIS USING CONTRAST ENHANCED ULTRASOUND

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Background: The optimum method to evaluate the efficacy of propranolol in cirrhotic patients with portal hypertension is the hepatic venous pressure gradient (HVPG) measurement. Measurement of pulse and blood pressure has not been shown to reflect portal haemodynamic changes. An accurate non-invasive method would be desirable. By contrast, measurement of hepatic transit times enhanced ultrasound has shown promise in the evaluation of liver disease.

Aim: To compare the hepatic transit times with the HVPG in the assessment of the acute haemodynamic response to propranolol in patients with cirrhotic portal hypertension.

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	HVPG (mm Hg)	HA (secs)	HV (secs)	ITI (secs)	Pulse /min	MAP (mm Hg)
T0	16.8 (4.3)	12.5 (4.4)	19.1 (6.5)	6.6 (3.2)	89 (12)	88 (11)
T90	13.4 (2.6)	16.6 (6.8)	25.8 (9.6)	9.1 (3.3)	80 (5)	84 (11)

Results shown as mean (SD).

Patients and Methods: We studied eight male cirrhotic patients (four Child-Pugh grade B and four grade C) with portal hypertension and varices. HVPG and hepatic transit time were measured before and 90 minutes after 80 mg propranolol orally. The transit time (defined as the time interval (seconds) between the start of the injection of 1 ml SonoVue into an anticubital vein and the first appearance of colour Doppler signal in the vessel), was recorded for the hepatic artery (HA) and hepatic vein (HV). The ''intrahepatic time index'' (ITI), defined as the difference between HV arrival time and HA arrival time was also evaluated.

Results: See table.

Conclusions: This pilot study shows that propranolol appears to prolong the HA, HV, and ITI. Hepatic transit times may offer a non-invasive method to assess response to propranolol in cirrhotic patients with portal hypertension.

336 INTERLEUKIN-1, TUMOUR NECROSIS FACTOR-α AND INTERFERON γ IN HEPATIC SCHISTOSOMIASIS: RELATION TO ERYTHROPOIESIS

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Background and Aim: Hepatic schistosomiasis is an immunoregulatory disease characterised by elaboration of various cytokines and is frequently associated with anaemia. Therefore, the present study was designed to determine the interrelationship between serum levels of interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), and erythropoiesis in this disease.

Methods: 38 patients with compensated schistosomal hepatic fibrosis (SHF) and 12 healthy subjects were included in the study. Serum IL-1β, TNF-α, and IFN-γ levels were measured using immunoenzymatic assay. Bone marrow (BM) was examined for cytological study and by Prussian blue stain to assess iron stores. Parameters of serum iron status (serum iron, transferrin saturation (Tfs), and serum ferritin) were also measured.

Results: Serum levels of IL-1β, TNF-α, and IFN-γ were significantly higher in patients with SHF than in control subjects ($p<0.05$). Bone marrow examination in the patients showed erythroid hyperplasia with late erythroid maturation arrest, a significant reduction in sideroblast percentage, and normal BM iron stores. These findings were associated with significant decreases in serum iron levels and Tfs and normal serum ferritin levels—that is, functional iron deficiency similar to the picture of ''anaemia of chronic disease''. Only serum levels of TNF-α showed positive correlation with the late erythroid maturation arrest and inverse correlation with serum iron levels, Tfs, sideroblast percentages, and haemoglobin concentrations in patients with SHF ($p<0.05$).

Conclusions: Hepatic schistosomiasis is associated with increased production of IL-1β, TNF-α, and IFN-γ. Only TNF-α seems to play a role in the suppression of late erythropoiesis, disturbance of iron status, and development of anaemia in this disease. This immune mediated mechanism has to be considered in the management of anaemia in patients with SHF.

337 BIOCHEMICAL AND CLINICAL PENETRANCE OF INDIVIDUALS DIAGNOSED WITH HAEMOCHROMATOSIS BY PREDICTIVE GENETIC TESTING

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Background: Genetic haemochromatosis (GH) is a common genetic disorder in white populations. However, the diagnosis of GH remains very low suggesting either underdiagnosis or low clinical penetrance.

Methods: We identified all individuals who were found to be either homozygous for the C282Y mutation, or compound heterozygotes for the C282Y and H63D mutations by predictive genetic testing between July 1997 and August 2003, after a relative was found to have GH. Data collected included patient history, known comorbidity, and laboratory results at diagnosis, together with the results of further relevant investigations.

Results: Fifty six individuals were identified, 27 (48%) of whom were male. Fifty one (91%) were homozygous for the C282Y mutation and the remaining five were compound heterozygotes. Mean age was 44.8 years. All 27 males had evidence of iron overload (ferritin ⩾300 μg or transferrin saturation ⩾45%) compared with 69% of females. The only compound heterozygote to have evidence of iron overload was male. Raised transaminase levels were found in 10 (37%) males and 2 (7%) females, all of whom had evidence of iron overload. To date, four individuals have undergone a liver biopsy, two of whom had hepatic fibrosis. Thirty seven individuals (66%) had a random glucose recorded at their first clinic visit, six of whom had a raised level. All of those with a raised glucose had evidence of iron overload. Of those with a full clinical history recorded, 68% were completely asymptomatic. Ten individuals (21%) complained of joint pains and a further nine (19%) complained of fatigue.

Conclusion: This study suggests that although biochemical penetrance of GH is high, the clinical penetrance is low.

338 PREVALENCE OF GENETIC HAEMOCHROMATOSIS AND IRON OVERLOAD AMONG PATIENTS ATTENDING RHEUMATOLOGY AND JOINT REPLACEMENT CLINICS

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Background and Aims: Genetic haemochromatosis (GH) is a common and underdiagnosed disorder, particularly affecting Celtic populations. Arthropathy is a common clinical expression. The aim of our study was to estimate the frequency of the HFE mutations (C282Y and H63D) and iron overload among patients attending the joint replacement clinic and new patients referred to the rheumatology clinic at our hospital and compare with a local control population.

Methods: Unselected patients attending the above clinics at Glasgow Royal Infirmary were anonymously tested for C282Y and H63D mutations. The patients also had (named) transferrin saturation and serum ferritin measured, and if elevated were called back for HFE mutation testing with predictive genetic counselling. For comparison, HFE mutation frequencies were determined from 340 controls.

Results: 161 unselected patients (71 attending the rheumatology and 90 the joint replacement clinics) were included in the study. The HFE mutation analyses are shown in the table.

There were no differences in the mutation frequencies or carrier rates between the rheumatology and joint replacement patients. One patient was found to be homozygous for C282Y (subsequently identified due to high serum ferritin) and eight were compound heterozygotes (one of whom had elevated transferrin saturation). Seven other patients had high ferritin, one of whom was heterozygous for the C282Y mutation.

Conclusion: The C282Y carrier frequency is significantly higher in patients attending the rheumatology and joint replacement clinics than controls. Screening of these patients for GH should be considered.

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	Patients	Controls	
Mutation frequency			
C282Y	10.2%	7.4%	NS
H63D	15.8%	15.5%	NS
C282Y carrier frequency	1 in 5.2	1 in 8.1	$p<0.05$

339 A PARADIGM SHIFT TOWARDS BLOODLESS LIVER SURGERY: RADIOFREQUENCY ASSISTED LIVER RESECTION OPTIMISES SAFETY AND MINIMISES BLOOD LOSS AND ICU ADMISSION

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Background: Various factors (eg recombinant activated factor VII infusion, topical haemostatic compounds, use of intraoperative ultrasonography, ultrasonic dissection, argon plasma coagulation, total vascular exclusion (TVE), the Pringle manoeuvre) have contributed to safety and accuracy in anatomical and non-anatomical liver resection. However, liver resection remains major surgery, and is associated with high peri-operative morbidity (10–39%) and mortality (0–8%), frequent need for intensive care unit (ICU) transfer, and a long postoperative stay (10–20 days). Excessive haemorrhage remains a major complication, and is associated with a postoperative mortality as high as 17%. We have recently described a new technique of potentially bloodless liver resection. It involves applying radiofrequency energy during surgery. We report its results in major liver resections for a variety of primary and secondary liver tumours.

Methods: Eighty five consecutive resections were performed using this novel radiofrequency assisted technique. The results were compared with a previous series of 80 liver resections from our group, in which the primary modalities used to limit liver blood loss were the standard, ubiquitous ones known as the Pringle manoeuvre (17.5% of cases) and TVE (76.3%).

Results: Median resection time was 60 min (30–140), and the median blood loss was only 50 mL (15–1500). The mean pre- and postoperative haemoglobin was 13.4 (SD 1.6) g/dL and 11.6 (SD 1.5) g/dL, respectively. Only 3 were admitted to ICU. The two postoperative deaths were unrelated to surgery. Postoperative mortality (2.35%) compares very favourably with the 7.5% observed in our previous series, in which currently established best surgical practice was observed. Overall complications (47.5 *v* 10.6%), blood transfusion (46.8 *v* 8.2%), biliary leaks (8.8 *v* 2.5%), ICU admission (83.8 *v* 3.5%), and postoperative stay (18.9 *v* 9 days) were all significantly reduced. Both series included metastases from colorectal cancer, primary hepatocellular carcinoma, cholangiocarcinoma, carcinoid tumours, gallbladder cancer, etc.

Conclusion: This novel technique of liver resection appears to be safer than currently accepted best surgical practice, is associated with loss, fewer biliary leaks, and other complications, a reduced postoperative stay in hospital, and a drastically reduced need for ICU admission.

340 OUTCOME OF SURGERY FOR GALL BLADDER DYSFUNCTION

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Background and Aims: The purpose of the study is to evaluate the outcome of laparoscopic cholecystectomy based on abnormal HIDA scan in the clinical setting of dysfunctional gall bladder. Cholecystectomy in the absence of gallstone(s) remains a controversial issue. There is no consensus as to how to manage these patients who continue to be symptomatic despite conservative measures.

Methods: 121 consecutive patients who had HIDA scan at Furness General Hospital, performed by single radiologist with special interest, were included in study. Further data were obtained from the case records including their presentation, mode of investigation, and treatment offered. Of these, the patients who had cholecystectomy were sent questionnaire to evaluate the outcome.

Results: Out of 121 patients who had HIDA scan, 65 (53.7%) were found to have unequivocal abnormal findings (no or reduced uptake, EF<35% at 30 minutes). Thirty one of these 65 patients finally underwent laparoscopic cholecystectomy. No complications were recorded. Histologically 26 (83.5%) of 31 gall bladders were found to be abnormal. Twenty seven patients returned the questionnaire. Of the 27 respondents 19 (61.3%) had significant improvement with 8 (25.9%) reporting full resolution of their symptoms. Six (19.3%) continued to have preoperative symptoms while 2 (6.4%) felt that they were worse after the operation.

Conclusions: In our experience laparoscopic cholecystectomy has proven to be an effective treatment in symptomatic patients with gall bladder dysfunction, demonstrated by abnormal HIDA scan. There is also a strong between abnormal HIDA scan and histological features of chronic cholecystitis.

341 MANAGEMENT AND OUTCOME OF BILE DUCT INJURIES COMPLICATING CHOLECYSTECTOMY

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Aims: To assess the management and outcome of bile duct injuries following cholecystectomy.

Methods: Patients referred to a regional HPB centre for iatrogenic bile duct injury over the last 7 years were identified retrospectively. Investigations, treatment, and outcome were recorded.

Results: 45 patients were identified. 25 injuries occurred during laparoscopic cholecystectomy, 10 following converted laparoscopic cholecystectomy and 10 during open procedures. Median time to diagnosis was 5 days (0–180). 12 were diagnosed intra-operatively. Presenting problems were: 18 collections, 15 cholangitis, 12 jaundice, 12 biliary fistulae, 6 abdominal pain. After laparoscopically initiated procedures, Strasberg classification of severity was: types A to D, 11; types E1 to E5, 23 (with E3 being the commonest). For open procedures, 2 were types A to D, while 7 were types E1 to E5. There was a tendency to more severe injury in the laparoscopic group. Six patients had associated vascular injuries with 3 having complete transaction of all three portal structures. Percutaneous drainage of collections was performed in 14, ERCP in 40, and PTC in 12. 37 patients underwent surgery. Three underwent major vascular reconstruction. One patient underwent a successful liver transplant and one died of ischaemic bowel and sepsis while awaiting a liver transplant. 31 Roux-en-y hepaticojejunostomies (4 with liver resections) and 1 choledochoduodenostomy were performed. Early complications of surgery occurred in 15 patients (8 major) with one death. Late complications occurred in 8.

Conclusion: The treatment of bile duct injury complicating cholecystectomy is demanding and carries significant risk of morbidity. Injuries tend to be more severe after laparoscopic procedures.

342 MANAGEMENT OF HILAR CHOLANGIOCARCINOMA (KLATSKIN TUMOUR): A SINGLE CENTRE EXPERIENCE

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Aim: To assess management and outcome of Hilar cholangiocarcinoma (Klatskin tumour) in a single tertiary referral centre.

Methods: All patient notes with a diagnosis of Hilar cholangiocarcinoma referred to our unit over a 7 year period were identified and retrospectively reviewed. Presentation, management, and outcome were assessed.

Results: 72 patients were identified. The median age was 64 yrs (range 34–84). Male to female ratio was 1:1.06. 90.2% of patients presented with jaundice. Most patients referred were Bismuth classification 3a, 3b, or 4. Seventy patients required biliary drainage. 65 patients required 152 percutaneous drainage procedures, 25 had complications. 41 patients were referred having had 51 ERCs performed (15 failed). Median number of drainage procedures for all patients was 3. (2 if resected, 3 if not resected ($p=0.038$)). 15 patients underwent resection (20.8%). 13 had complications and 3 died postoperatively. Five year survival was 10.9% for all patients, 42% in resected patients, and 3% in those not resected ($p<0.05$). Median number of admissions after diagnosis in resected patients was 2.5 and 3 in non-resected patients ($p<0.05$). There was no significant difference in CA19/9 levels between non-resected and resected patients. 10 patients had external beam radiotherapy, 7 brachytherapy, and 7 chemotherapy. These conferred no significant benefit in terms of survival or hospital admissions.

Conclusions: Resection increases survival but carries the risk of significant morbidity and mortality. There is no evidence of benefit from chemotherapy or radiotherapy in non-resected patients. Percutaneous biliary drainage is almost always necessary and ERCP should be avoided where possible.

343 ARE THE ROYAL COLLEGE OF PHYSICIANS' GUIDELINES ON THE USE OF PABRINEX IN CONFUSED ALCOHOLICS FOLLOWED IN CLINICAL PRACTICE?

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Introduction: Chronic, heavy alcoholic users are at risk of Wernicke's encephalopathy (WE), but clinical features are difficult or impossible to differentiate from drunkenness. Untreated patients are at risk of long term brain injury.

Aim: To establish current practice in a large district hospital in using Pabrinex in confused alcoholics and whether the Royal College of Physicians' (RCP) guidelines on prevention and treatment of WE are followed.

Methods: A prospective audit over a 2 month period (June–July 2003) in a district general hospital. Every day admitting teams (medicine, surgery, orthopaedics) were questioned for confused alcoholics and case notes surveyed within 48 hours.

Results: A total of 44 patients (32 male) with indication for Pabrinex according to RCP guidelines were admitted, 84% under medical care. The main indications were confusion/sepsis, seizure, major GI bleed, alcoholic hepatitis, withdrawal, and intoxication. Only 59% (26/44) of patients received ''any'' Pabrinex; under the surgeons only 43% (3/7). In 3 cases Pabrinex was prescribed, but not given. 91% (40/44) of the total patients received an incorrect regimen or none. 38% (11/29) of patients received just a ''one off'' dose. The correct TDS regime was prescribed in only 14% (4/29) of patients. The ''door-to-needle'' time was >6 hours in 50% (13/26).

Conclusions: (1) RCP guidelines for the prevention of WE were not followed in a substantial proportion of patients. (2) Pabrinex was not given at all in over a third of cases where it was indicated. If prescribed, it was an incorrect regimen in the majority. Pabrinex was given late in half of the patients. (3) Local Pabrinex guidelines (following the RCP) should be created for all acute admissions of alcohol abusers. These should be regularly audited.

344 CASE FATALITY AND MORBIDITY IN PATIENTS WITH ALCOHOLIC LIVER DISEASE

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Background: Alcoholic liver disease (ALD) is a heterogenous condition, in terms of its presentation, clinical course, and mortality. Available data on mortality at the national level show a rising trend in the UK in the face of a steady fall in many other European countries. Very few data are, however, available from the individual trust hospitals.

Methods: A study was carried out in a district general hospital serving a catchment population of approximately 290 000 and typical of the UK population. Using 18 categories of ICD10 diagnostic codes for ALD, a total of 211 patients directly related to ALD as a primary diagnosis over a period of 12 months were identified. There were a total of 11 256 acute medical admissions during that period. The relevant medical case notes were studied to confirm diagnosis and evaluate the management and outcomes. Death notification data from the office of National Statistics Office were also used. An age and sex matched control group was selected from those admitted to the Medical Admission Unit with non-ALD types of illness during the same period.

Results: The median length of stay for patients with ALD was 7 days. 5% stayed more than 30 days and 1% stayed for more than 90 days. 20% of patients self discharged against medical advice. 18% had further admissions within the 12 month period.

Survival status could not be ascertained in 16 ALD and 12 non-ALD patients. The overall case fatality rate amongst the ALD patients was 21%. This compares with 6% for the control group. Although 75% of admitted ALD patients were male the 12 month fatality rates were 17% for males and 24% for females.

Comment: Mortality was higher in ALD than in non-ALD patients. In the absence of comparative data from other trusts it is difficult to comment on the mortality figures further. Similar analyses shared across organisations may be useful in enabling a greater understanding of the natural course of the illness and identification of regional differences in outcome that may influence the outcome of treatment given to these patients.

345 LIVER IRON GRADE IN DECOMPENSATED ALCOHOLIC LIVER DISEASE: PROGNOSTIC SIGNIFICANCE AND RELATION TO HFE GENOTYPE

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Background: Moderate liver iron accumulation is common in alcoholic liver disease (ALD). Its causation is poorly understood but it has been associated with a poor outlook (Ganne-Carre, *Gut* 2000;**46**:277).

Aim: To determine factors associated with liver iron in decompensated ALD.

Patients: 78 patients (50 male, mean age 44 (SD 11) years) with alcohol consumption >60 U/wk (M) or 40 U/wk (F) for >5 yr,

decompensated (Child B or C) liver disease, serology not suggestive of chronic viral or autoimmune liver disease and liver histology (72 biopsies, 2 explants, 5 postmortem), obtained median (range) 56 (2–2195) days after decompensation, consistent with ALD. Liver iron was graded 0–4 using Pearls staining and the method of Scheuer. Relations were assessed between iron grade and other histological parameters, HFE genotype (performed in 69 patients), and patient survival following first recorded decompensation.

Results: Grade 0, 1, 2, 3, and 4 iron was found in 41, 20, 12, 5, and 0 of the 78 patients respectively. Iron was seen in hepatocytes in 34 patients, biliary cells in 5, and Kupffer cells only in 2. Liver iron grade showed no association with any of: (a) time post decompensation when biopsy performed, (b) presence of cirrhosis (n = 59), steatosis (n = 60), neutrophilic infiltration (n = 37), Mallory's hyaline (n = 44), or ballooning degeneration (n = 55), severity of liver dysfunction at decompensation or at biopsy. Liver iron grade distribution did not differ between patients without HFE mutations (n = 39), and patients heterozygous for C282Y (n = 8) or H63D (n = 18) mutations. Of those with grade 3 iron, two were C282Y heterozygotes and three were wild/wild. Survival rates 1 and 5 years following initial decompensation were 84+4% and 64+9% respectively and showed no association with liver iron grade by either univariate or multivariate life table analysis.

Conclusion: In decompensated ALD, moderate liver iron accumulation is common but is of limited clinical significance.

346 PROSPECTIVE STUDY TO ASSESS MAGNESIUM STATUS IN PATIENTS PRESENTING WITH ALCOHOL WITHDRAWAL SEIZURES

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Introduction: Chronic alcohol abuse is a well recognised cause of magnesium deficiency. Hypomagnesaemia is a known metabolic cause of seizures, which are also a feature of the alcohol withdrawal syndrome. The significance and possible role of magnesium depletion in patients with alcohol related fits is not yet clear. There are features that are similar to the refeeding syndrome.

Aims: We sought to assess the magnesium status in chronic alcohol abusers particularly those admitted with withdrawal seizures.

Patients and Method: We recruited the patients presented to the admission ward at our hospital with alcohol related seizures (group I) during the period of the study (March–September 2002). Age and sex matched groups of patients with chronic alcoholic liver disease (group II) and patients known with grand mal epilepsy (group III) were also included in the study as controls. All patients had serum magnesium measured on admission that was corrected for serum albumin by a standard and validated method. All patients had CT head scan and measurement of serum electrolytes, calcium, and blood sugar upon admission.

Results: 55 patients (37 males) were recruited; 15 in group I, 19 in group II, and 21 in group III.

Serum magnesium was significantly low in group I *v* group II ($p<0.05$) and *v* group III ($p<0.001$) using one way analysis of variance (Kruskal-Wallis test). None of the other parameters showed significant difference among the groups.

Conclusion: Low serum magnesium may have a causal effect alcohol related seizures.

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Group	Mean (95% CI) magnesium	Sodium	Mean potassium	Calcium
I	0.683 (0.6–0.76)*	134.8	3.69	2.26
II	0.807 (0.73–0.89)	133.8	3.69	2.28
III	0.865 (0.81–0.92)	137.8	4.2	2.23

347 VITAMIN D DEFICIENCY IN ALCOHOLIC LIVER DISEASE

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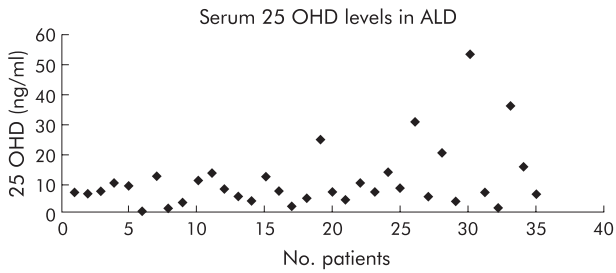
Introduction: Vitamin D deficiency is very common in patients with alcoholic liver disease (ALD) but frequently goes unrecognised. It occurs due to a number of factors including inadequate exposure to sunlight, lack of dietary support, and impaired absorption of vitamins due to cholestasis. It often presents with non-specific symptoms such as limb pains and backache, and remains a reason for poor mobilisation in many ALD patients. Despite being such a common problem, there are very few data about vitamin D deficiency in these patients.



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Methods: Blood samples were taken from all patients with ALD who were admitted through MAU or to the ward. Serum hydroxycholecalciferol (25 OHD), serum 1,25 OHD, alkaline phosphatase (ALP), and calcium phosphate levels were measured.

Results: Vitamin D deficiency is indicated by 25 OHD levels of <15 ng/ml; levels <5 ng/ml indicate severe deficiency.

Most patients (86%) were deficient in 25 OHD; 25% had a severe deficiency. 42% of patients also had low levels of 1,25 OHD. There was no correlation between serum ALP and 25 OHD, therefore ALP cannot be used as a surrogate marker for vitamin D deficiency. Calcium phosphate was within normal range in the majority of the patients. Following treatment with vitamin D and calcium, most patients felt better and mobilised earlier.

Conclusions: The majority of ALD patients were found to be severely deficient in vitamin D. Based on these findings we suggest that vitamin D levels are checked routinely in all ALD patients before treatment is started.

348 AN AUDIT OF THE MANAGEMENT OF SEVERE ALCOHOLIC HEPATITIS IN A DISTRICT GENERAL HOSPITAL

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Background and Aim: Severe alcoholic hepatitis is an increasingly common condition associated with a high mortality rate of over 40% at 1 month. The conventional treatment includes complete abstinence and aggressive nutritional support. Steroids have been shown to be beneficial in controlled studies in a subgroup of patients with a particularly poor prognosis as identified by a Maddrey's discriminant function (DF) value of greater than 32 and/or spontaneous encephalopathy. The aim of this audit was to investigate current outcomes of severe alcoholic hepatitis in a district general hospital (DGH) where transjugular liver biopsies are routinely performed and patients treated with steroids in addition to standard treatment.

Methods: We retrospectively studied all patients with a proven histological and clinical diagnosis of severe alcoholic hepatitis from 1 January 2002 to 31 June 2003. A review of medical records including follow up for a mean of 10 months (range 4–18) was conducted.

Results: Thirteen patients were identified, with data unavailable in one case. Of the 12 analysed 10 were male and the mean age was 47.1 years (range 26–63). 10 patients (83%) received steroid therapy in conjunction with standard treatment. The remaining 2 patients did not due to active gastrointestinal bleeding and DF<32 respectively. Prednisolone therapy was initiated at a dose of 40 mg daily on the basis of clinical assessment and the DF whilst awaiting results of the liver biopsy. This was performed as a transjugular procedure in all patients due to the presence of coagulopathy +/− ascites. The mean DF in the treatment group was 52.6 (range 34–82). In 11/12 patients (91.6%) histological features of cirrhosis, in addition to alcoholic hepatitis, were present. At 30 days only 1 of the 12 patients had died (8.3%).

Conclusions: Severe alcoholic hepatitis can be successfully treated in a DGH setting, with the availability of transjugular liver biopsy, resulting in favourable outcomes compared with published data.

349 AUDIT OF THE MANAGEMENT OF VARICEAL BLEEDING IN A SINGLE UNIT

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Background: Recent clinical studies of endoscopic and pharmacological treatments have reported reduced mortality (14–24%) and rebleeding rates (12–35%) in patients with varices.

Aims and Methods: To assess if similar outcomes can be achieved outside of the setting of a clinical trial, a retrospective audit of all patients with variceal bleeding admitted to our unit between 1 November 2001 and 31 May 2003 was conducted.

Results: There were 93 admissions for 70 patients with variceal bleeding to the unit; the age (mean (range)) was 53 (21–80) years. 51 patients (55%) presented with their first bleed whilst 19 patients had their first variceal bleed before the audit period. 49 admissions were directly to the Bleed Unit, 44 were referred from neighbouring hospitals. One patient had portal vein thrombosis only, the remainder had chronic liver disease. Child-Pugh Grade: A, 10; B, 47; C, 36 patients. The Child-Pugh score was 8.94 (5–14). The length of stay on the bleed unit was 7.5 days (1–41). Management strategies included terlipressin, prophylactic antibiotics, and emergency endoscopy. 72 patients were transfused; the transfusion requirement was 3.8 units (1 to 17).

Gastroscopy was performed within 24 hours in 76 (82%) patients. 25 (27%) were bleeding actively at endoscopy. 77 (83%) received treatment (banding, sclerotherapy, histoacryl glue injection). Seven patients bled from gastric varices, the reminder had oesophageal varices. Seven patients (7.2%) required insertion of a Minnesota tube. Eight patients (8.3%) required HDU/ITU admission. Two patients (2.2%) were operated upon. Two patients (2.2%) were transferred for TIPSS, of which one was transplanted and the other received further endoscopic therapy. In-hospital mortality was 8.2%. The in-hospital rebleeding rate was 17% (15.7% in those with their index bleed during the audit period and 26.3% in those with who had bled before the audit period). 27.1% were readmitted with rebleeding during the audit period (31% in patients who had bled before the audit period and 25% in those who had not).

Conclusion: The improved mortality from variceal bleeding found in several new studies could be replicated in the clinical practice. It is likely that the use of terlipressin, prophylactic antibiotics, and therapeutic endoscopy, as well as a dedicated GI bleed unit contributed to the improved survival.

350 SURVIVAL IN UNSTABLE VARICEAL HAEMORRHAGE IS RELATED TO EARLY ENDOSCOPIC INTERVENTION

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Introduction: Acute variceal haemorrhage is associated with high short term mortality. Endoscopic and pharmacological treatments have been advocated in this setting but not all hospitals have emergency haematemesis teams experienced in treating varices.

Aim: The aim of this study was to review the management of acute variceal haemorrhage and identify those treatments associated with a favourable outcome.

Methods: This was a retrospective case note review of patients presenting with variceal haemorrhage over a 30 month period. 125 episodes of upper GI bleeding with oesophagogastric varices (OGV) were identified. Of these 70 were haemodynamically unstable on admission and/or had active bleeding or stigmata of haemorrhage at endoscopy without another bleeding source identified (''unstable OGV'').

Results: The overall 6 week mortality was 23%; for unstable OGV it was 36%. Mortality for Child's C patients was greater than that for A/B patients (44% *v* 18%; $p<0.05$). The 6 week rebleeding rate was 20%. The table shows 6 week survival for ''unstable'' patients relative to treatment.

Conclusions: This study emphasises the importance early endoscopic therapy for OGV haemorrhage. Other forms of treatment may be of lesser relevance if effective endotherapy can be administered. This has implications for the provision of emergency endoscopy for upper GI haemorrhage.

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	Survivors (n = 45)	Non-survivors (n = 25)
Endotherapy at initial endoscopy	26 (58%)* (Child's C: 70%)	7 (28%)* (Child's C: 38%)
Vasoconstrictor drug use	29 (64%) (Child's C: 60%)	17 (68%) (Child's C: 69%)
Antibiotic use	22 (49%) (Child's C: 70%)	14 (56%) (Child's C: 75%)

*$p<0.05$

351 OUTCOMES IN PATIENTS WITH CYSTIC FIBROSIS AND VARICEAL HAEMORRHAGE

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Introduction: Autopsy and imaging studies show that liver involvement is common in cystic fibrosis. Complications of liver disease, however, are reported in less than 5% and variceal haemorrhage is uncommon. The impact of variceal haemorrhage on prognosis in cystic fibrosis is unclear. Because of this uncertainty patients have been recommended for liver transplantation (if pulmonary function is preserved) or for heart/lung/liver transplantation in preference to heart/lung transplantation on the basis of a history of variceal haemorrhage.

Methods: The Cystic Fibrosis Department database contains records on 1154 adult patients from 1981 onwards. This was screened for cases of variceal bleeding. The case notes were examined and details were collected on bleeding history, survival, and cause of death.

Results: 19 patients had suffered bleeding due to oesophageal or gastric varices (1.6% of the database). The median age at first bleed was 20.8 years (range 9.7–30.8). One patient had a liver transplant 8.0 years after the index bleed and remains alive 4.3 years later. Three other patients remain alive 8.4, 10.3, and 13.2 years after the index bleed. 15 patients have died a median of 9.0 years (0.1–21.8) after the index bleed. The median age at death of these patients was 25.8 years (19.6–36.3). Nine patients died of respiratory disease with no discernible contribution from their liver disease. Liver disease contributed to 5 deaths. One further patient suffered a fatal haemorrhage that was either variceal or bronchial in origin; otherwise no patient died directly from variceal haemorrhage.

Conclusion: Long term survival is common in patients with cystic fibrosis following variceal haemorrhage. This finding suggests that, in the absence of features of hepatic decompensation, liver transplantation is not indicated and these patients should not be excluded from heart/lung transplantation.

352 TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPSS) IN THE TREATMENT OF ECTOPIC VARICEAL BLEEDING

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Background: Bleeding from ectopic (rectal and stomal) varices is a well recognised complication of portal hypertension. There are few data in the literature on managing such problems and the optimal treatment for rectal varices has yet to be established. Transjugular intrahepatic portosystemic shunt (TIPSS) has been used in the treatment of ectopic varices.

Methods: We retrospectively reviewed our institution's experience of patients with ectopic variceal bleeding who underwent TIPSS for recurrent bleeding not responding to conservative management.

Results: Over an 11 year period (1992–2002) we identified eight patients who underwent TIPSS for ectopic variceal haemorrhage. Four patients bled from rectal varices and 4 from stomal varices. TIPSS was successful in seven patients: the one failure being due to an anatomical abnormality of the portal vein. There were four males and three females with a mean age of 60.5 years (range 43–73 years). The Child-Pugh grade of the patients was A = 3, B = 2, and C = 2. The follow up period range from 7 days to 46 months. TIPSS successfully controlled bleeding in all patients. Rebleeding occurred in three patients two of whom died. The remaining patient had a blocked TIPSS and successfully underwent repeat stenting which re-established patency. Four patients (Child's B = 2, Child's C = 2) died within 60 days of TIPSS due to multiorgan failure. All of these four had a significantly elevated bilirubin (mean = 30 mgs/dl) and/or a raised creatinine (mean = 3.3 mgs/dl) with advanced Child-Pugh grades. All three patients with Child's A liver disease were alive at one year.

Conclusion: In our experience TIPSS can be used effectively to treat ectopic variceal bleeding. In this small series, patients with Child's grade A liver disease appear to do well with TIPSS. Those with advanced liver disease (Child's B and C) have a uniformly poor outcome, particularly when associated with renal impairment.

353 TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTING (TIPSS): ELEVEN YEAR EXPERIENCE AT A REGIONAL REFERRAL CENTRE

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Background: Since 1988, TIPSS has been widely promoted as a treatment for uncontrolled variceal bleeding and refractory ascites. We present an eleven year review of TIPSS in a tertiary referral centre.

Aims and Methods: The aim of this retrospective analysis was to study the efficacy of TIPSS and to look at five year survival of all patients who underwent TIPSS between 1992 and 2002.

Results: 124 patients had 148 procedures performed during the study period. Of these the procedure failed in eight patients because of technical difficulty. Seventy three (63%) patients were referred from 13 hospitals in our region. Mean age of the group was 51.5 years (range 18–87 years) and 59% were male. Portal hypertension was caused by alcoholic liver disease in 81% with viral hepatitis B or C being an additional aetiology in 11 (12%) of these patients. 92% of patients presented with variceal bleeding while the rest were patients with refractory ascites. The Child-Pugh score of the patients was A = 13%, B = 24%, and C = 63%. The mean pre TIPSS portal pressure gradient was 21.5 mm Hg (range 10–48 mm Hg) and the mean post TIPSS portal pressure gradient was 7.7 mm Hg (range 0–16 mm Hg). Thirty eight patients (33%) had 46 episodes of rebleeding. Twenty five (66%) of the patients who rebled had repeat TIPSS performed. Seventy two (62%) patients have died over the follow up period. Survival of Child's A and B was significantly better than Child's C patients ($p = 0.03$) but there was no significant difference between A and B. Of the patients who died, recurrent bleeding was the cause of death in 16 (22%) whilst multiorgan failure was the most common mode of death (70%).

Conclusion: TIPSS is effective in controlling variceal bleeding. Multiorgan failure is the most common cause of death in this mainly alcohol related patient group. Mortality rates remain high in Child C patients.

354 TIPSS FOR REFRACTORY ASCITES: ARE THE TRIALS WRONG?

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Methods: TIPSS has been compared to large volume paracenthesis (LVP) in 4 randomised controlled trials with mostly poor results. We performed TIPSS in 49 carefully selected cirrhotic patients with refractory ascites (15 patients with ascitic hydrothorax were excluded). 38 were male, mean age at procedure was 58.1 years and mean Child-Pugh score 9 (SD 1.6). Aetiology was alcoholic liver disease (62%), HCV (8%), cryptogenic (8%), and other (22%). Portal pressure gradient was reduced from a mean 20.7 (SD 5.2) mm Hg to 12.0 (SD 4.6) mm Hg. Limited initial stent dilatation was performed irrespective of portal pressure reduction, in order to minimise the risk of hepatic encephalopathy (HE): mean dilatation diameter was 7.9 (SD 1.8) mm. Complete response was defined as absence of clinically detectable ascites without need for further LVP, partial response as continued presence of ascites without further need of more than 1 LVP per month. Patients were followed up for a mean of 265 (SD 387) days.

Results: Complete response at 1, 3, 6, and 12 months was present in 21, 46, 59, and 73% of patients alive respectively; presence of either complete or partial response was present in 70, 92, 94, and 100%. 14 patients died after a median of 33 days, 7 of these within the first 8 days. Seven patients underwent orthotopic liver transplantation. An episode of HE after TIPSS occurred in 23 patients (47%), but these were mostly grade 1–2 (75%) and responded fully to medical treatment in all but 4 patients. Further procedures were required in 35% of patients. During follow up, compared with baseline, urea and creatinine levels were lower at 1 and 3 months and Child score lower at 3, 6, and 12 months ($p<0.05$).

Conclusions: TIPSS can be an effective procedure for highly selected patients with refractory ascites and may improve renal and liver function in addition to providing symptomatic relief. Use of smaller diameter dilatation may reduce the severe complications associated with TIPSS whilst maintaining efficacy, and may explain the failure of TIPSS in the recently published RCTs.

355 A SINGLE CENTRE EXPERIENCE OF PTFE COVERED STENTS: A TIPSS REVOLUTION

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Background: TIPSS has improved the management of portal hypertension but shunt insufficiency occurs in up to 50% of standard stents within a year. Recent reports suggest that the polytetrafluoroethylene (PTFE) covered stents improve both short and long term patency.

Aims: This large retrospective study aims to examine the impact of covered stents, particularly in shunt insufficiency.

Methods: A single centre review of 100 patients who have had PTFE covered stents (Viatorr Gore) placed either at the time of index TIPSS (91%), or at follow up to re-stent an uncovered stent showing recurrent stenosis, (9%). The aetiology was alcoholic liver disease in 67%. Mean age was 52.4 (13.2) years. All TIPSS were checked by direct portography at 6 monthly intervals, and intervention performed if required.

Results: The average follow up period was 10.0 (SD 12.3) months. The portal pressure gradient fell from 21.9 (SD 6.5) to 6.8 (SD 4.3) mm Hg (index TIPSS group) and from 21.6 (SD 8.5) to 6.9 (SD 4.8) mm Hg (re-stent group) following TIPSS insertion. Mean Child-Pugh score in the whole group was 9.9 (SD 2.2). TIPSS was performed as a result of an uncontrollable variceal bleed in 84.3% of cases. 15.7% of patients had a shunt placed for refractory ascites. Shunt insufficiency, as defined by a PPG >12 mmHg, occurred in only 8% of covered stents. The variceal rebleeding rate was 9.5%. All patients in this rebleeding group, where portography was performed, had insufficient TIPSS). The estimated probability of survival without transplantation was 61% at 1 yr. Post-TIPSS hepatic encephalopathy occurred in 29% of patients (de novo encephalopathy in 16%).

Conclusions: Our experience suggests that the PTFE covered stent has an improved primary patency rate in comparison to the standard uncovered stent. The variceal rebleeding rate is low, and rates of hepatic encephalopathy are comparable to standard stents. The use of PTFE covered stents may significantly reduce the need for invasive portographic follow up.

356 AN AUDIT OF LIVER BIOPSY IN CLINICAL PRACTICE

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Introduction: Liver biopsy has become one of the central investigations for investigation of hepatic disease. In 1991 there was a national audit which demonstrated wide differences in practice. This led to the BSG guidelines being issued in 1999 to standardise practice across the UK.

Aims: To examine if clinical practice for liver biopsy within North Bristol NHS Trust adhered to BSG recommendations.

Methods: Case notes for patients undergoing liver biopsy between January 1999 and May 2001 were examined, looking at indications, pre-assessment, consent, method of biopsy, morbidity, and mortality.

Results: There were 172 biopsies in total. 127 (74%) were performed at Frenchay Hospital and 45 (26%) at Southmead. 73% were performed as inpatient, 27% as outpatient procedure. Commonest indications for procedure were for investigation of abnormal LFT (47%), followed by neoplasia (44%), and chronic HCV (8%). Types of liver biopsy were as follows: blind 22%, guided 74%, transjugular 0%, laparoscopic 4%. Prebiopsy investigations recorded confirmed platelet (94%) and PT (94%) checked beforehand. 93% had INR <1.4, 99% had platelets >60 000 mm^3. 83% had prebiopsy ultrasound. Whereas 90% case notes yielded a signed consent form, 19% had additional documentation re the risks/benefits had been given to the patient. Majority of biopsies were performed by consultant grade (63%), followed by SpRs (35%). Number of passes undertaken were as follows: 3 passes (18%), 2 passes (32%), and 1 pass (50%). Abdominal pain (11%) was the most common complication with total post biopsy complication rate of 14% overall. Only 4 cases required hospital admission. There was no correlation with operator grade and number of complications after liver biopsy. 4% patients died within 30 days of the procedure, with one further patient dying within 42 days. 0.006% deaths could be directly attributed to the procedure.

Conclusions: The data collection form was completed retrospectively and not always completed. This may reflect on accuracy of audit. Morbidity mainly abdominal pain at 14% exceeds national morbidity rate 5.9% but mortality directly attributed to the procedure at 0.006% was lower that national rate of 0.1 and 0.01%. Where coagulopathy had been recorded, correction had been undertaken, and in some

instances given for measurements outside BSG recommendations. Areas identified for recommendations were that informed consent should be obtained with documentation of benefit and risk given to patient, to limit the number of passes when undertaking a liver biopsy, and that correction for coagulopathy and thrombocytopaenia should be given as per guidelines. The majority of these changes have been adopted. A liver biopsy patient information leaflet has been drafted and is under discussion for use in North Bristol NHS Trust, referring for a guided liver biopsy with no more than 2 passes attempted. The procedure is discussed with the patient when attending the specialist liver clinic. Benefits, risks, and mortality discussed are recorded, with further written information to confirm these by letter closer to time of procedure.

357 ACUTE LIVER FAILURE IN SCOTLAND: AN OBSERVATIONAL STUDY 1992–2003

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Introduction: Acute liver failure is an uncommon clinical problem. The causes and outcomes differ in different populations. The provision of a single liver transplantation unit in Scotland has allowed study of acute liver failure in a relatively stable defined population.

Methods: Patients with acute liver failure referred to the Scottish Liver Transplantation Unit (SLTU) were prospectively entered (November 1992–September 2003) into a database and the results analysed using SPSS statistical package.

Results: Between November 1992 and September 2003, 633 patients were admitted to the SLTU with acute liver failure (ALF). The most common of cause of ALF was paracetamol poisoning (487 patients, 76.9%), followed by non A–E hepatitis (54 patients, 8.5%), and idiosyncratic drug reactions (29 patients, 4.6%).

In patients with paracetamol poisoning 142 (29%) fulfilled the King's College poor prognostic criteria (pH $\leqslant$7.3 or Grade 3 or 4 hepatic encephalopathy, PT $>$100 seconds, serum creatinine $>$300 umol/L). However, only 59 (41.5%) of these patients were considered candidates for transplantation. 19 patients (32.2%) died before transplantation became available. In the transplanted patients 27 (67.5%) survived to be discharged from hospital. In contrast with the patients with paracetamol poisoning, those with non-paracetamol ALF had a worse prognosis, 68 patients' (46.6%) cases fulfilled the King's College poor prognostic criteria and more of these patients were considered candidates for transplantation (50 patients, 73.5%). However similar numbers of patients died before transplantation became available (11 patients, 22%) and survived to discharge following the operation (28 patients, 56%).

Conclusions: The frequency of paracetamol poisoning as a cause of ALF is the highest reported, compared with other populations throughout the world. Patients with paracetamol poisoning have a better prognosis than those with non-paracetamol ALF, but significantly fewer of these patients will be considered for transplantation if they fulfil poor prognostic criteria.

358 GLYCINE AMELIORATES THE EARLY PHASE OF LIVER WARM ISCHAEMIA REPERFUSION INJURY IN A RABBIT MODEL

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Background: Liver ischaemia reperfusion injury (IRI) is a major complication of liver resection and transplantation. Cytokine release by activated Kuppfer cells (KC) plays a central role in this inflammatory response. Glycine a non-essential amino acid may protect against liver injury by inhibition of KC activity.

Materials and Methods: A rabbit model of hepatic lobar warm I/R was used. Under general anaesthesia, the sham group (n=6) underwent laparotomy alone for seven hours. The control I/R group (n=6) underwent 60 min of left and median lobe inflow occlusion and 6 hrs of reperfusion. The glycine I/R group (n=6) underwent a similar procedure after receiving a single dose of glycine 5 mg/kg intravenously. Systemic haemodynamics, portal blood flow, bile flow, hepatic microcirculation (by laser Doppler flowmeter) and intracellular tissue oxygenation (by near infrared spectroscopy) were recorded. TNFα was measured in serum samples at one, two, four, and six hours after ischemia by ELISA.

Results: Results are expressed as mean (SD). On reperfusion, the glycine group demonstrated increased bile flow (145.0 (11.4) *v* 108.3 (28.2) μL/min/gm in controls, $p<0.05$), portal blood flow (95.6 (18.6) *v* 62.5 (19.3) mL/min in controls, $p<0.001$), hepatic microcirculation (220.6 (25.0) *v* 151.6 (46.0) Flux units, $p<0.05$) and the hepatic intracellular tissue oxygenation (-13.8 (6.7) *v* -25.5 (7.7) Δ units; $p<0.05$) compared with the control group. A significant reduction of circulating TNFα was seen in the glycine group at one (187 (118) pg/ml *v* 283 (99) pg/ml; $p<0.01$), two (203 (111) pg/ml *v* 267 (58) pg/ml; $p<0.01$) and four (198 (96) pg/ml *v* 330 (116) pg/ml; $p<0.01$) hours post ischemia. However there was no significant difference at six hours (335 (102) pg/ml *v* 297 (104) pg/ml; $p>0.05$).

Conclusions: Intravenous glycine administration reduces the hepatic hemodynamic alterations and suppresses TNFα release induced by liver IRI and may provide a novel therapeutic modality.

359 INCREASED FORMATION OF NITROSOTHIOLS FOLLOWING WARM LIVER ISCHAEMIA REPERFUSION INJURY

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Background and Methods: Plasma nitrosothiols (RSNOs) may act as a circulating form of nitric oxide (NO) that affects vascular function and platelet aggregation. Their role in liver ischaemia/reperfusion (I/R) injury is largely unknown. The present study has investigated the changes in plasma nitrosothiols, nitrite/nitrate (NO_2^-/NO_3^-) levels, hepatic parenchymal microcirculation, and intracellular tissue oxygenation in the rabbit lobar I/R model. Lobar liver ischaemia was induced in the I/R group (n=6) for 60 min, followed by 7 hours of reperfusion. Sham group (n=6) underwent laparotomy but no liver ischaemia. Serial RSNOs levels were measured in plasma by electron paramagnetic spectroscopy (EPR), NO_2^-/NO_3^- plasma levels by electrophoresis, hepatic microcirculation by laser Doppler flowmetry, and tissue cytochrome oxidase by near infrared spectroscopy. Results were expressed as mean (SD). A p value of <0.05 was considered significant.

Results: There was significant increase in RSNOs levels 5 hours post-reperfusion in I/R group compared with baseline (539 (204) *v* 202 (165) nM). At the same time points there was a significant decrease in microcirculation (152 (32) *v* 208 (29) flux units) and in cytochrome oxidase levels (-25.5 (7.6) *v* 0.3 (1.8) μmol/L). The changes in NO_2^-/NO_3^- plasma levels were not significant (43.6 (7.6) *v* 51.4 (4.8) μM). There were no significant changes in RSNOs levels in the sham group.

Conclusions: The increased RSNOs concentration at 5 hrs post reperfusion correlates negatively with changes in microcirculation and oxygenation showing that there is marked upregulation of NO synthesis during I/R injury. Measurement of RSNOs levels is a better marker of NO activity than NO_2^-/NO_3^- plasma levels.

360 PROTON MAGNETIC RESONANCE SPECTROSCOPIC ASSESSMENT OF BILE PRODUCED DURING NORMOTHERMIC EXTRACORPOREAL PERFUSION BY HEARTBEATING AND NON-HEARTBEATING DONOR LIVERS

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Background: Organs retrieved from marginal and non-heartbeating donors (NHBD) have sustained variable degree of preretrieval damage and result in increased incidence of complications. Normothermic extracorporeal liver perfusion (NELP) provides an opportunity to evaluate and resuscitates such organs. Aim of this study was to study the bile produced during retrival and perfusion by livers from heartbeating donors (HBD) and NHBDs for markers of ischaemic injury.

Methods: Livers were retrieved from New Zealand white rabbits. HBD group (n=4) no in situ warm ischaemia before retrieval and NHBD group (n=4), 45 minutes of in situ warm ischaemia before liver retrieval. After 40 minutes of post-retrieval cold ischemia, all livers were dual vessel reperfused normothermically with oxygenated buffer solution supplemented with rabbit red blood cells for 6 hours. Bile was collected and examined with ^{1}HMRS.

Results: Perfusion bile from HBD group showed increased concentration of bile acids, lactate, glucose, and phosphatidylcholine, but

decreased concentration of acetate compared with retrieval bile. This trend was further enhanced in NHBD group. The mean (SD) in μmol/l were bile acids (10.48 (2.8) *v* 26.05 (12.1) *v* 44.5 (44.5)), lactate (10.66 (4.5) *v* 14.66 (5.2) *v* 13.22 (1.8)), glucose (5.37 (2) *v* 21.2 (5.0) *v* 29.09 (15.3)), phosphatidylcholine (0.21 (0.02) *v* 5.57 (1.7) *v* 6.42 (0.3)) and acetate (1.8 (0.5) *v* 0.39 (0.1) *v* 0.38 (0.09)) for retrieval bile, HBD perfusion bile, and NHBD perfusion bile respectively. One animal from each group did not produce any bile during perfusion.

Conclusions: ^{1}HMRS of biliary constituents reveals differences with type of ischaemia. These indices may be potential markers of the extent of warm ischaemic injury and functional activity of the extracorporeally perfused liver.

361 NORMOTHERMIC EXTRACORPOREAL PERFUSION OF NON-HEARTBEATING DONOR LIVERS. METABOLIC AND HAEMODYNAMIC ASSESSMENT

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Background: Deficiency of transplantable organs has renewed interest in non-heartbeating donors (NHBD). Such organs have sustained variable degree of warm ischaemic damage and their viability may be suboptimal. Normothermic extracorporeal liver perfusion (NELP) provides an opportunity for liver evaluation and possible optimisation during the period between organ retrieval and implantation. The aim of this study was to evaluate liver haemodynamic and metabolic activity during NELP in NHBD and heart beating donor (HBD) models.

Methods: Livers were retrieved from New Zealand white rabbits. NHBD group (n = 4), underwent 40 minutes of in situ warm ischaemia before liver retrieval. HBD group (n = 4) no in situ warm ischaemia before retrieval. All livers were subjected to 40 minutes of cold ischaemia after retrieval. All livers were dual vessel reperfused, normothermically with oxygenated buffer solution supplemented with rabbit red blood cells for 6 hours. Haemodynamics, and metabolic activity were examined at regular intervals.

Results: Perfusate sodium concentration in NHBD group were significantly lower than the HBD group (149.50 (1.24) *v* 155.93 (2.24) mmol/l, p = 0.005) while perfusate glucose concentration in NHBD group was significantly higher than the HBD group (32.30 (5.03) *v* 24.46 (2.0) mmol/l, p = 0.020). Portal flow was significantly lower ($p<0.001$) and portal resistive index was higher (p = 0.013) in the NHBD group.

Conclusions: NHBD damage is reflected in reduced perfusate sodium concentration and increased perfusate glucose concentration. Similarly in situ warm ischaemia increases portal resistance and reduces portal flow. These indices may be potential markers of the extent of warm ischaemic injury and metabolic activity of the extracorporeally perfused liver.

362 FIVE YEAR FOLLOW UP OF IMMUNE SUPPRESSION WITH SIROLIMUS FOR LIVER TRANSPLANTATION

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Introduction: The first study using sirolimus for primary immunosuppression after liver transplantation, initially for hepatic malignancy, was reported in 1999. Many of these patients did not meet transplant criteria outside a trial situation. We now report on the 5 year follow up data of these patients.

Methods: Notes of patients were reviewed to determine survival, outcome after transplantation for hepatocellular carcinoma (HCC), changes in renal function, effect on hepatitis C, and side effects.

Results: Of 27 patients entered into the study, 13 (48%) are still alive at 5 years compared with 85% of patients who were not in the trial. Of these, 6 continue to take sirolimus in the long term, 7 having changed to a calcineurin inhibitor. In a univariate analysis of outcome, survival of patients with HCC was improved by treatment with sirolimus for at least 3 months, odds ratio 6.94 (95% CI 1.38 to 34.92, p = 0.019). There was however no difference seen on multivariate analysis. Renal function of surviving patients taking sirolimus in the long term compared to controls taking a calcineurin inhibitor was significantly better at 4 and 5 years post transplantation (p = 0.037). Patients with hepatitis C had a lower rate of fibrosis progression compared to contemporaneous controls, but due to small numbers this was not significant. No patient developed chronic rejection on sirolimus. One patient is taking a statin for high cholesterol and also treatment for hypertension. One patient had a re-transplant for chronic liver abscesses. Treatment was withdrawn in 11 of the original 27 patients because of side effects, but the doses used are now regarded as too high.

Conclusion: Patients taking sirolimus instead of a calcineurin inhibitor for their primary immunosuppression have better renal function after 5 years and improved survival if transplanted for HCC, although sirolimus may not be an independent risk factor. There may be slower progression of hepatitis C related fibrosis. There were no problems related to chronic rejection or other long term side effects.

363 IMPROVEMENT IN RENAL FUNCTION AFTER SWITCH TO SIROLIMUS

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Introduction: Following liver transplantation, long term immunosuppression with tacrolimus and cyclosporin is associated with renal impairment in up to 83% of patients at 3 years and renal replacement therapy required in up to 9% of patients at 13 years. Withdrawal of calcineurin inhibitor therapy often results in improvement in creatinine, but may also predispose to acute rejection. Sirolimus is an immunosuppressant which does not act by calcineurin inhibition, is equipotent with cyclosporine and tacrolimus, but is not nephrotoxic.

Methods: 17 liver transplant recipients had their calcineurin inhibitor (CNI) substituted with sirolimus monotherapy at 6–83 months because of nephrotoxicity (creatinine range 123–244 μmol/l). Renal function, systolic blood pressure, uric acid, and lipid levels were recorded before changing immunosuppression and after 2 years. 13 (76%) continued on sirolimus monotherapy long term. Four (24%) discontinued sirolimus because of side effects.

Results: 9/13 (69%) patients able to continue sirolimus had a lower serum creatinine 2 years after changing from a CNI to sirolimus and 1 had died. Only 1 had a significant progressive deterioration of renal function. There was little difference in the other parameters (see table).

Conclusion: 69% of patients showed an improvement in serum creatinine 2 years after changing to sirolimus. In this context, renal impairment is usually progressive and this represents a marked improvement over continuing CNI. There was a high (24%) incidence of side effects causing discontinuation of sirolimus but at doses now regarded as excessive. There were no long term problems in those continuing sirolimus over 2 years.

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	Creatinine	BP	Uric acid	Cholesterol	Triglyceride
Median	−26	−11	0	0.1	0.5
IQR	−42 to −2	−21 to 9	−0.08 to 0.07	−0.7 to 1.3	0.2 to 0.9

364 DOSE OF TACROLIMUS REQUIRED TO MAINTAIN THERAPEUTIC LEVELS DECREASES POST LIVER TRANSPLANT IN HEPATITIS C (HCV) RECIPIENTS

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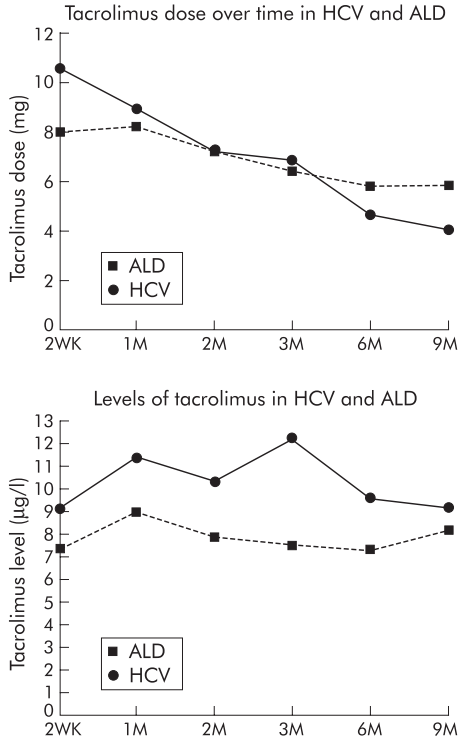
Introduction: Following orthotopic liver transplantation (OLT) graft re-infection by HCV is universal. We have noticed that a progressively lower dose of tacrolimus is required post-OLT to maintain a constant tacrolimus level in individual patients transplanted for HCV. In this study we compared tacrolimus dose and level in subpopulations transplanted for HCV infection and alcoholic liver disease (ALD).

Methods: Tacrolimus dose and level and plasma creatinine were collected from all HCV (n = 15) and ALD (n = 26) patients transplanted between 1 January 2001 and 31 December 2002. Data were assessed at the following intervals: 2 weeks; one, two, three, six, and nine months post-OLT and compared between the two groups by repeated measures analysis. Hepatitis C recurrence was confirmed by liver biopsy in patients who had a raised transaminase level.

Results: The dose of tacrolimus required to maintain a therapeutic level decreased more rapidly over time in the HCV patients compared with the ALD patients (p = 0.001) (fig 1). The HCV group also had a significantly higher tacrolimus level compared with the ALD group

(p=0.002) (fig 2) although there was no difference in the trend over time (p=0.14). Creatinine values were similar in the two groups.

Conclusion: Liver transplant recipients with HCV require significantly lower doses of tacrolimus over time to achieve therapeutic levels, compared with recipients transplanted for ALD. The liver injury resulting from graft reinfection by HCV may be lead to decreased hepatic clearance of tacrolimus by HCV transplant recipients.



365 LIVER TRANSPLANT RECIPIENTS OLDER THAN 60 YEARS HAVE LOWER SURVIVAL AND HIGHER INCIDENCE OF MALIGNANCY

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Introduction: Older age is not considered a contraindication for liver transplantation, but age related morbidity may be a cause of mortality.

Aim: To evaluate survival and the incidence of main post-transplant complications in orthotopic liver transplant recipients ⩾60.

Patients and Methods: From 1988 to October 2003, 767 adult liver transplants were performed at the Royal Free Hospital. Patients were divided in two groups according to age and compared. Re-transplants (n=72) were excluded from the analysis.

Results: Group A <60 years (n=597): % M/F 61/39; group B ⩾60 years (n=98) % M/F 52/48. Commonest aetiologies (group A/B) in %: HCV 21/36 (p=0.001), HBV 10/8, ETOH 19/8 (p=0.017), PBC 20/25 (p=0.033), PSC 14/6, concomitant malignancy 17/25 (p=0.0003). No patient ⩾60 underwent OLT for acute liver failure. Main complication group A/B in %: rejection 87/48, HAT 6/3, biliary leak operated 0.3/3.0 (p=0.02), biliary stricture 1/6 (p=0.008). There were no statistical differences for infections. Overall survival A/B in % 68/63, survival at 1 year 84/66 (p=0.001), and at 3 years 84/65 (p=0.001). Survival for HCV 35/31, malignancy overall survival 8/64 (p=0.0001).

Conclusion: Older patients were more frequently transplanted for hepatitis C, hepatocellular carcinoma, and PBC, whereas younger patients were more commonly transplanted for ETOH. Biliary complications were more common in older patients. After transplantation, older patients had a significantly lower survival at 1 and 3 years, with no difference between sexes. The lack of difference in overall survival may represent a cohort effect, with fewer older patients transplanted at the start of the programme. Older patients transplanted for liver malignancy had a better survival reflecting probable selection bias. With more elderly patients being referred for transplantation, careful assessment remains paramount to maximise outcome.

366 IMPROVEMENT IN COGNITIVE FUNCTION FOLLOWING LIVER TRANSPLANTATION: A PROSPECTIVE STUDY

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Introduction: Patients with chronic liver disease frequently experience cognitive dysfunction. The effect of liver transplantation on this dysfunction is uncertain.

Methods: Consecutive patients attending St James's University Hospital for transplant assessment were invited to participate in the study. Patients with grade 2 or greater hepatic encephalopathy were excluded. Cognitive function was assessed using a battery of neuropsychological tests, including the Mini-Mental State Examination (MMSE), the Rey Auditory-Verbal learning test (RAVLT), Trail-making tests, the Stroop test, and the Benton Visual Retention test (BVRT). Health related quality of life was assessed using the EuroQol. The Hospital Anxiety and Depression Scale was used to screen for anxiety and depression. This assessment was repeated 3–6 months after transplantation. Twenty five healthy volunteers were recruited as controls.

A 10% change in cognitive function scores was defined as clinically significant, giving a sample size of 50. The study was approved by the local research ethics committee.

Results: Fifty eight patients were recruited but 8 died post-transplant. The median age at transplantation was 51.5 years (IQR 44–58 years) and patients had spent a median of 11 years (IQR 10–16 years) in education. The commonest indications for transplantation were alcoholic liver disease (n=18) and primary biliary cirrhosis (n=15).

There was a significant improvement (p<0.001) across all the areas of cognitive function tested. Patients did not return to normal however, and performed significantly worse post-transplant than the control group on all tests other than verbal learning and trail A. Self rated health related quality of life and levels of anxiety also improved (p<0.01).

Conclusion: Cognitive function and health related quality of life in patients with end stage liver disease improve following liver transplantation, but do not return to normal. The test used commonly on liver units (trail A) may fail to detect continued impairment.

367 CARDIOVASCULAR MORTALITY AND MORBIDITY POST LIVER TRANSPLANTATION

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Background and Aims: The incidence of coronary artery disease in patients undergoing liver transplantation suspected to be between 5–10%. The American College of Cardiology (ACC) have issued guidelines aimed at identifying patients at risk of coronary artery disease. The aims of our study were (1) to determine the incidence of cardiovascular (CV) mortality and morbidity in patients undergoing orthotopic liver transplantation (OLTx) and (2) to evaluate the potential use of ACC clinical predictors as a guide for further cardiac investigation.

Methods: We studied retrospectively 111 consecutive patients who had a liver transplant for chronic liver disease and a postoperative follow up of 6 months between 13 July 2000 and 31 December 2002. Their cardiac risk factors were identified at assessment. Predictors of cardiac risk were defined as two or more of the following (obesity, hypertension, smoking, increased cholesterol, cardiac family history, age >50) or one of the following (abnormal echo, LBBB, ST, T wave changes or a rhythm other than sinus, previous MI or CVA).

A CV event was defined as a myocardial infarction, angina, unexplained pulmonary oedema, arrhythmia, cardiac failure, and cardiac arrest.

Results: The majority of those transplanted had alcoholic liver disease (25%) or primary biliary cirrhosis (16%). Mean (SD) age (54.5 (1.1)), mean (SD) BMI (26.8 (0.6)), 21% of patients had a BMI >30, 21% were smokers, 19% had type II DM, and 12% were hypertensive. Twelve patients (10.8%) died during follow up, two (16.7%) deaths were due to CV events (MI and CCF). Non-fatal CV events occurred in 15 (13.5%) patients during follow up. Preoperatively 60% (67/111 patients) were at high risk of CV events, but only 65% of CV events (11/17) during 6 months occurred in this group and 35% (6/17) in the low risk group (p>0.5).

Conclusions: CV events are surprisingly uncommon within 6 months of liver transplantation considering the predicted high risk of our

population. In addition the proposed American College of Cardiology clinical predictors of cardiovascular risk do not identify a population at higher risk of CV events following liver transplantation and if applied would result in a large number of unnecessary invasive investigations.

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368 MICROBIAL MANNAN SUPPRESSES MACROPHAGE KILLING OF BACTERIA: A MECHANISM FOR GRANULOMATOUS INFLAMMATION IN CROHN'S DISEASE

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Background: Crohn's disease (CD) 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. The CD associated NOD2/CARD15 defect that is present in a minority of CD cases is known to result in defective killing of phagocytosed bacteria (Hisamatsu, *et al. Gastroenterology* 2003;**124**:993–1000). We have speculated that bacterial mannan might induce an acquired defect in phagocyte bacterial killing. We previously reported that oligomannan inhibits the neutrophil respiratory burst in a dose dependent manner, and also inhibits the monocyte respiratory burst. We have now assessed the effect of mannan on bacterial killing by monocyte derived macrophages (MDM).

Methods: Human peripheral blood mononuclear cells were purified from heparinised venous blood by a one step centrifugation method using PolymorphPrep. Monocytes were isolated from this population by adherence to plastic and matured into MDM by culturing for 5–7 days in RPMI medium supplemented with 10% L-glutamine, 2% fetal calf serum, and 50 U/ml granulocyte macrophage colony stimulating factor. Mature MDM (1×10^5/ml) were cultured with *Staphylococcus aureus* (Oxford strain) 1×10^6/m in the presence or absence of *S cerevesiae* mannan. Bacterial killing was assessed by culture at 24 h following hypotonic lysis.

Results: The presence of *S cerevesiae* mannan 1 mg/ml resulted in a 63 (SD 13) % reduction in killing of bacteria by MDM at 24 h ($p=0.015$, $n=3$ experiments).

Conclusion: These results support the hypothesis that microbial mannan may act as a pathogenic factor in non-familial Crohn's disease by causing an acquired impairment of phagocyte function within the intestinal mucosa.

369 CLINICAL AND FUNCTIONAL SIGNIFICANCE OF VITAMIN D RECEPTOR POLYMORPHISMS IN INFLAMMATORY BOWEL DISEASE

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Background and Aims: Vitamin D receptor (VDR) maps to a candidate region for inflammatory bowel disease (IBD) and has *Apa1*, *Taq1*, and *Fok1* coding region polymorphisms. Downstream consequences and clinical significance of these polymorphisms are unknown. This study assesses VDR polymorphisms against clinical manifestations of IBD and seeks effects on expression of VDR and the VDR downstream gene, osteopontin (OPN).

Methods: Genomic DNA was extracted from 218 IBD patients (146 ulcerative colitis (UC), 67 Crohn's disease (CD), 5 indeterminate colitis) and 181 controls from the genetically stable population of Northern Ireland. Thirty two IBD patients also had colitis associated colorectal neoplasia (27 cancer, 5 dysplasia). DNA was genotyped for *Apa1*, *Taq1*, and *Fok1* polymorphisms. Potential associations with clinical manifestations or complication of IBD were investigated. Allelic linkage disequilibrium was assessed. Effects of VDR polymorphisms on VDR and OPN expression was assessed, by semiquantitative RT-PCR.

Results: Homozygous *Fok1* polymorphisms (''ff allele'') associated with colitis associated colorectal neoplasia (CACRN) (frequency = 0.29 *v* 0.12 control; $p=0.024$. Homozygous *Taq1* polymorphisms (''tt allele'') associated with CD (frequency = 0.30 *v* 0.12; $p=0.001$). In a subset of 10 patients, the ff allele associated with decreased OPN expression although VDR expression was unaffected. Linkage disequilibrium was observed between *Apa1* and *Taq1*.

Conclusions: VDR polymorphisms have downstream effects upon target gene expression and clinical significance in IBD. The Fok1 ff allele links to CACRN. The Taq1 tt allele associates with Crohn's disease.

370 PRESENCE OF HELICOBACTER AND ENTEROTOXIGENIC BACTEROIDES FRAGILIS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background and Aim: Inflammatory bowel disease (IBD) is a multifactorial and heterogenous disease, in which a particular pathogen or the commensal microflora could be the stimulus. Some evidence exists to relate *Helicobacter* species and enterotoxigenic *Bacteroides fragilis* (ETBF) to the pathogenesis of disease. Our aim was to determine if either of these two putative pathogens was linked to disease in our population of patients.

Patients and Methods: We investigated 35 patients with IBD (11 Crohn's disease, 20 ulcerative colitis, and 4 indeterminate), of which 27 had active disease and 37 control patients (19 with diarrhoea and 18 without diarrhoea). DNA was extracted from luminal washings and colonic biopsies. The presence of *Helicobacter* species and *Bacteroides fragilis* enterotoxin was determined by PCR with the use of primers specific for *Helicobacter*-16S ribosomal RNA and enterotoxin gene, respectively.

Results: After PCR, sequencing and Blast search, the presence of *Helicobacter* species was confirmed in 3 patients with IBD and 3 control patients. *Helicobacter pylori* were found in one patient, using glmM primers. Six out of 14 patients with diarrhoea (42.9%) and 4 out of 14 patients without diarrhoea (28.6) had positive luminal washing for the *Bacteroides fragilis* enterotoxin. The enterotoxin was found in the luminal washing of 8 out of 32 patients with IBD (25%). In the IBD group, the enterotoxin was found more often in patients with active disease (28%) compared with patients with no active disease (14.3%) although the difference was not statistically significant ($p=0.64$).

Conclusion: The colon does not seem to be a natural habitat for *Helicobacter* species whereas the prevalence of ETBF in our population is high. However, neither of these two pathogens appear to be linked to either IBD or diarrhoea in our population of patients.

371 GENERATION OF IL-1 RECEPTOR ANTAGONIST, IL-10, SOLUBLE TNF-α RECEPTORS I AND II DURING ADSORPTIVE GRANULOCYTE AND MONOCYTE APHERESIS TREATMENT OF PATIENTS WITH ACTIVE ULCERATIVE COLITIS

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Introduction: Active ulcerative colitis (UC) is associated with increased peripheral blood granulocytes and monocytes/macrophages. Further, faecal calprotectin (a neutrophil protein) level parallels intestinal inflammation and can predict UC relapse (*Gastroenterology* 2000;**119**:15–22). Accordingly, adsorptive granulocyte and monocyte apheresis (GMA) in patients with severe UC was associated with a dramatic and sustained clinical efficacy (Hanai H, *et al. Clin Gastroenterol Hepatol* 2003;**1**:28–35). However, the full efficacy of GMA does not appear to be due to the reduction of peripheral blood granulocytes and monocytes per se.

Aims and Methods: We were interested to see if GMA changes the plasma levels of substances which might exert anti-inflammatory effects. Forty six patients with steroid dependent UC, mean CAI 9.2 and DAI 8.6 were treated with GMA by using the Adacolumn which removes granulocytes and monocytes (Fcγ and complement receptors expressing leucocytes). During the first treatment session, we measured plasma levels of IL-1 receptor antagonist (IL-1ra), IL-10, soluble TNF-α receptors I and II, and L-selectin expression index on leucocytes at the inlet to the column and in the blood returning to the patients (column outflow).

Results: In the column outflow, the levels of IL-1ra, IL-10, TNF-α receptors I and II increased by 96% ($p=0.0001$), 322% ($p=0.0001$), 56% ($p=0.0001$), and 51% ($p=0.0001$), respectively together with down modulation of L selectin ($p=0.0001$). In the same test samples, TNF-α and IL-1β were virtually undetectable. IL-1ra and IL-10 are reported to have strong anti-inflammatory effects, while soluble TNF-α receptors are known to block the effect of TNF-α in vivo.

Conclusions: The major sources of IL-1ra, IL-10, TNF-α receptors I and II are believed to be adsorbed monocytes and neutrophils to the column

carries. These effects, together with reduction of circulating levels of granulocytes and monocytes, should alleviate inflammation. The results should increase understanding of the mechanisms of clinical efficacy associated with adsorptive granulocyte and monocyte apheresis.

372 ADSORPTIVE GRANULOCYTE AND MONOCYTE APHERESIS VERSUS PREDNISOLONE IN PATIENTS WITH CORTICOSTEROID DEPENDENT ULCERATIVE COLITIS

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Introduction: Corticosteroids are given to induce remission in patients with active ulcerative colitis (UC), but frequent relapse is common in patients who initially respond. Further, prolonged steroid therapy has been considered unwarranted because of frequent steroid side effects. Therefore, there is a need for steroid free treatment of UC. However, increased granulocyte and monocyte/macrophage levels, activation behaviour and prolonged survival time is a feature of active UC and mucosal granulocyte level parallels intestinal inflammation and can predict UC relapse (Tibble JA, *et al. Gastroenterology* 2000;**119**:15–22). We thought that adsorptive granulocyte and monocyte apheresis (GMA) therapy to reduce the circulating level of these leucocytes might reduce inflammation and prevent relapse during steroid tapering in steroid dependent (SD) patients. In this study, we evaluated the clinical efficacy GMA with the view to reduce steroid dose.

Methods: Sixty nine SD patients, at the time of relapse were randomly assigned to groups I (n=46) and II (n=23). The mean dose of prednisolone (PSL) was 12 mg/day per patient, CAI (clinical activity index) 9.2 and DAI (disease activity index) 8.6 in both groups. Group I patients were given up to 10 GMA sessions of 60 minutes duration over 10 weeks with Adacolumn, while in group II, the mean dose of PSL was increased to 30 mg/day per patient.

Results: At week 12, 83% of group I and 65% of group II patients were in clinical remission, CAI and DAI in group I were 1.7 ($p<0.001$) and 2.8 ($p<0.001$) respectively and in group II, 2.5 ($p<0.001$) and 2.9 ($p<0.001$) respectively. Further, during the 12 weeks of treatment, the cumulative amount of PSL received per patient was 1157 mg in group I and 1938 mg in group II ($p=0.001$).

Conclusions: Leucocytes produce cytokines that can initiate and perpetuate inflammatory diseases and therefore, should be the logical targets of therapy of active UC. Accordingly, GMA appeared to be an effective adjunct to standard drug therapy of active UC by promoting remission and suppressing relapse during steroid tapering.

373 BENEFICIAL EFFECTS OF PREBIOTICS, GERMINATED BARLEY FOODSTUFF IN THE LONG TERM TREATMENT OF ULCERATIVE COLITIS: A MULTICENTRE OPEN CONTROL STUDY

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Background: Germinated barley foodstuff (GBF) is a prebiotic foodstuff that effectively increases luminal butyrate production by stimulating the growth of protective bacteria. In our previous study, GBF has been shown to reduce both clinical activity and mucosal inflammation in active ulcerative colitis (UC). The aim of this study was to investigate the efficacy of GBF in long term UC treatment in a multicentre open control trial.

Methods: This research was approved by the ethical committee of respective institutes, and informed consent was obtained from all patients. Study 1: 22 UC patients in remission period were given daily 20–30 g of GBF together with the baseline treatment for 6 months. The control group received only base line anti-inflammatory treatment (n=39) was settled. The response to treatments was evaluated by clinical activity index (CAI by Rachmilewitz, Sandborn index), the degree of reduction of steroidal drugs, and incidence of recurrence. Study 2: 15 active UC patients (mild to moderate) were given GBF in the same way as study 1. The efficacy of GBF was evaluated CAI and serological parameters, compared with initial periods.

Results: Study1: after 6 months, CAI in GBF group was significantly lower than that in initial period (3.5 (SD 0.7*) *v* 1.5 (SD 0.5)) and that of control group (1.8 (SD 0.6*) *v* 3.2 (SD 0.5)). The incidence of recurrence in GBF was 5.2%*, and 23% in control group, after 6 month. Study 2: after 6 months CAI significantly decreased, compared with that of the initial period (1.5 (SD 0.2*) *v* 4.5 (SD 1.0)) . There were no significant differences in all serological parameters between the initial period and 6 month treatment. *$p<0.05$.

Conclusion: Oral GBF treatment may have the potential to prolong the remission period, in addition to decreasing CAI during the active period. We believe that these results support the use of GBF administration as a new adjunctive UC treatment.

374 WITHDRAWN

375 SYNERGISTIC EFFECTS OF SYSTEMIC TREFOIL FACTOR FAMILY 1 AND EPIDERMAL GROWTH FACTOR IN A RAT MODEL OF COLITIS

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Background: Treatment of inflammatory bowel disease is suboptimal and novel treatments are required. We examined the potential value of the trefoil peptide TFF1 and EGF alone and in combination in an in vitro restitution assay and a rat model of colitis.

Methods: Effects of TFF1-Cys^{58}+/−EGF on an in vitro wounding model of restitution were determined using HT29 cells. Animals had colitis induced by adding 4% dextran sulphate sodium (DSS) to drinking water for 7 days. Animals also received twice daily s.c. injections of EGF (600 μg/kg), native TFF1-Cys^{58} protein or TFF1-Ser^{58} analogue (both 100 μg/kg), or EGF plus TFF1-Cys^{58} starting 2 days before DSS administration (n=7–16 per group). Disease activity was assessed using histological scoring of inflammation and tissue myeloperoxidase activity.

Results: TFF1-Cys^{58} and EGF had synergistic activity in the in vitro assay. Treatment with TFF1-Cys^{58} alone reduced colitis score by 22% ($p<0.02$ *v* DSS alone) but TFF1-Ser^{58} variant was ineffective. In a second study, TFF1-Cys^{58} reduced histological score by 14% (*v* DSS alone), EGF by 26% and a synergistic response was demonstrated when used together (42% reduction *v* DSS alone and $p<0.01$ *v* either peptide given alone). Similar results were seen when assessing MPO activity.

Conclusion: Systemic administration of TFF1 reduces DSS induced colitis and Cys^{58} is important in this effect, probably by allowing dimerisation. Synergistic effects were seen when co-administered with EGF. Although caution must always be shown when considering administering factors with pro-mitogenic or pro-angiogenic activity, where appropriate, this approach may be particularly useful for colitis in patients with disease extending beyond the reach of topical therapy.

376 CORTICOSTEROID THERAPY AS A RISK FACTOR FOR SERIOUS ABSCESS IN NON-OPERATED CROHN'S DISEASE

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Introduction: Corticosteroid therapy may be a contributory factor to septic complications of Crohn's disease.

Aim: To assess the association between prior corticosteroid therapy and the formation of intra-abdominal or pelvic abscess.

Methods: A retrospective case control study was performed. Forty eight cases of perforating Crohn's disease were identified from our database. Four with postoperative perforating disease and three without clear corticosteroid history were excluded. Corticosteroid therapy in patients with intra-abdominal or pelvic abscess was compared with steroid therapy in patients with perianal disease and/or fistula diagnosed during the same time period (first analysis). A second analysis restricted to patients presenting since 1998 used, as control, patients with active non-perforating disease defined by HB index >4. For the latter controls steroid therapy within 3 months after disease relapse was compared with steroid usage in the 3 months prior to identification of abscess.

Results: See table (first analysis).

This shows an increased risk of major abscess formation in association with prior steroid usage when compared with other forms of perforating Crohn's disease ($p=0.03$, OR 10.4 95% CI 1.19 to 91.2). Among patients presenting after 1998, 7/7 patients with abscess received systemic corticosteroids compared with 7/15 controls with active non-

perforating disease and 7/15 with fistulating and/or perianal disease (p = 0.02).

Conclusion: Corticosteroid therapy is a risk factor for intra-abdominal and pelvic abscess in Crohn's disease.

Abstract 376

	Pelvic/intra-abdominal abscess (n = 13)	Perianal disease (n = 16)	Other fistula (n = 12)
Smoking	6/12 (1 not known)	6/16	3/12
Steroid therapy in preceding 3 months	12/13 (prednisolone, median dose 20 mg)	8/16 (median 20 mg)	7/12 (median 15 mg)

377 THE ECONOMIC IMPACT OF INFLAMMATORY BOWEL DISEASE ON RADIOLOGICAL SERVICES

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Background: Inflammatory bowel disease (IBD) patients undergo radiological investigations for diagnostic purposes, to define the extent of disease and for detecting complications. The economic burden of IBD on radiological resources is not well defined.

Aims and Methods: To study all radiological procedures undergone by IBD patients over a 5 year period. Data for all radiological procedures carried out on IBD patients from January 1998 to October 2002 were obtained from a prospective IBD database and hospital records.

Results: 596 patients (301 UC and 295 CD) were identified to have had various radiological procedures done over a 5 year period. The median age for UC was 53 yrs (17–98) and 46 yrs (18–91) for CD. There was an average of 120 (83–154) admissions per year, of which 65% were for exacerbations. Over the 5 year period, a total of 974 radiological investigations were performed. This included 433 (252 UC and 181 CD) abdominal *x* rays (AXR), 225 (103 UC and 122 CD) abdominal ultrasounds (USG), 27 (14 UC and 13 CD) CT abdomen, 95 (53 UC and 42 CD) barium enemas (BE), 171 (49 UC and 122 CD) small bowel enemas (SBE), and 23 pouchograms (PGM) were done. Table 1 illustrates the number of patients who had radiological investigations performed every year. Over this period 65% (44% UC and 21% CD) also had endoscopic investigations done. 16% of UC and 20% of CD patients required surgical interventions. Of those who underwent surgery, 40% of UC and 31% of CD required more than one operation

Conclusion: IBD patients pose a considerable economic burden on radiological services. The most frequent investigations carried out being AXR (44%), USG (23%), SBE (18%), and BE (10%). Despite these, 65% of the patients will still also require endoscopic investigations.

Abstract 377 Number of patients who had radiological investigations per year

	AxR	USG	CT	B enema	SB enema	PGM
1998	26	32	4	20	19	3
1999	46	35	3	12	30	2
2000	67	46	3	20	39	5
2001	57	26	6	20	29	5
2002	26	16	1	9	15	3
Total	232	155	17	81	132	18

378 BASILIXIMAB FOR THE TREATMENT OF STEROID RESISTANT ULCERATIVE COLITIS

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Introduction: Steroid resistance in ulcerative colitis (UC) presents a difficult clinical challenge, with few available therapeutic options other than colectomy. Basiliximab is a chimeric monoclonal antibody to the IL-2 receptor (CD25) which has potential as a new treatment for this condition. We have previously shown its effect as a steroid sensitiser in steroid resistant UC, both in vitro and in vivo.[1] We now present an extended series of 30 steroid resistant UC patients treated with basiliximab in an uncontrolled pilot study.

Methods: 20 patients with moderately active disease despite at least 14 days of ⩾30 mg prednisolone (Ulcerative Colitis Symptom Score (UCSS) ⩾6), and 10 patients with severe disease (Truelove and Witts criteria) with either poor predictors of outcome at day 3 of intravenous (IV) hydrocortisone 400 mg/day or incomplete response after 7 days of IV hydrocortisone were treated. All patients received a single IV dose of 40 mg of basiliximab in addition to their standard steroid treatment. Primary end point was remission within 8 weeks defined by a UCSS ⩽2. Secondary end points included the Inflammatory Bowel Disease Questionnaire (IBDQ).

Results: Moderate group: 14/20 patients (70%) achieved full remission, 5/20 (25%) showed an improvement in UCSS, 1/20 (5%) required ciclosporin. Severe group: 5/10 patients (50%) achieved remission, 5/10 (50%) required colectomy. Overall: 24/30 patients (80%) improved their UCSS score, with 19/30 (63%) achieving full remission. Median IBDQ increased from 110.5 (IQR 92 to 129) at week 0, to 177 (IQR 153 to 184) at week 8 ($p<0.0001$). There were no infusion reactions. Adverse events included herpes zoster in 2 patients.

Conclusion: Treatment with basiliximab in combination with steroids achieved an improvement in 95% and remission in 70% of patients with moderate steroid resistant UC. Overall, an improvement in 80%, and remission in 63% was seen in patients with moderate and severe steroid resistant UC within 8 weeks. A large randomised controlled trial is needed to confirm these promising uncontrolled data.

1. **Creed TJ**, *et al. Aliment Pharmacol Ther* 2003;**18**:65–75.

379 PROXIMAL CONSTIPATION IN DISTAL ULCERATIVE COLITIS: IS IT A SLOW TRANSIT PHENOMENON?

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Background: Up to 25% of patients with distal ulcerative colitis (UC) complain of hard stools in association with blood and mucus, a sensation of incomplete evacuation, and straining at defaecation. This is attributed to stasis in the right colon, evident as faecal loading on a plain abdominal *x* ray. There are no colonic transit data to support the use of either fibre or non-osmotic laxatives as treatment.

Aim: To conduct a randomised trial of fibre (Fybogel) *v* non-stimulant osmotic laxative (Movicol) in patients with constipation and distal colitis with assessment of pre- and post-treatment symptom response and colonic transit.

Patients and Methods: Consecutive patients with active or quiescent distal UC were screened for constipation using the Thompson criteria. Patients were assessed using the Cleveland Clinic Constipation Score questionnaire followed by a colonic transit study (St Mark's Protocol). Patients ingested a set of 6 marker capsules over 3 consecutive days followed by an abdominal *x* ray on day 6. Slow transit constipation and segmental distribution of markers was recorded. A second assessment and transit study was carried out after 4 weeks of treatment.

Results: 14 patients were studied between May–October 2003; all had faecal loading in the right colon on a plain abdominal *x* ray. The mean constipation score was 8.6 (range 4–16). 11 patients had a normal transit while the remaining 3 patients had slow transit constipation on marker studies. Of these 3 patients, none had retention of markers in the right colon; most markers were distributed in the left colon or in the rectosigmoid region. Symptom response to treatment will be analysed when the study concludes in January 2004, and the randomisation code is broken.

Conclusion: This study indicates that colonic transit in the majority of patients with distal UC and constipation is normal; a minority have delayed transit in the left colon and rectosigmoid. There appears to be normal motility on the right side of the colon.

380 DENDRITIC CELLS MAY DRIVE PROINFLAMMATORY T CELL IMMUNE RESPONSES IN CROHN'S DISEASE BY PRODUCTION OF IL-12 AND IL-6

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Introduction: Dendritic cells (DC) are antigen presenting cells that are unique in their ability to activate naïve T cells and shape the developing T cell response to be immunogenic or tolerogenic. DC produce cytokines such as IL-12 which polarises a Th1 response, IL-10 which influences a regulatory response, and IL-6 which may play a role in overcoming the suppressive effect of regulatory T cells. We assessed production of these cytokines by gut DC in inflammatory bowel disease.

Methods: Mononuclear cells were obtained by collagenase digestion of endoscopic biopsies from 9 patients with Crohn's disease (CD), 6 patients with ulcerative colitis (UC), and 10 controls. DC were identified as a CD11c+HLA−DR+lineage−(CD3-, CD14-, CD16-, CD19-, CD34-, CD56-) population by multicolour flow cytometry. Cytokine production (IL-12, IL-6, and IL-10) by DC in a 4 hour culture in the absence of exogenous stimulation was assessed by intracellular staining.

Results: IL-12 was produced by a significantly higher proportion of DC isolated from CD (48% (SD 6%)) than from UC (18% (SD 12%)) or control samples (9% (SD 5%)). There was no detectable IL-6 production by DC from control biopsies, but a significant proportion of DC from both CD (46% (SD 9%)) and UC (23% (SD 9%)) tissue produced IL-6. DC from UC and CD tissue did not differ significantly from each other with regard to IL-6 production. A small proportion of DC from all types of tissue produced IL-10 and there was no significant difference between DC from patients or controls.

Conclusions: Production of cytokines by colonic DC is altered in active intestinal inflammation. In CD, enhanced production of proinflammatory IL-12 by DC may underlie the pathogenic Th1 response that characterises this disease. Elevated IL-6 production by DC in intestinal tissue may play a role in the anti-apoptotic pathway or in inhibiting the function of regulatory T cells.

381 THE EFFECT OF NITRIC OXIDE ON COLONIC EPITHELIAL CELLS

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Introduction: In ulcerative colitis, upregulation of inducible nitric oxide synthase occurs in colonic epithelial cells along with increased production of nitric oxide (NO). We investigated the potential toxicity of NO to colonic epithelial cells.

Methods: HT29 cells were cultured with the NO donor DETA NONOate (NOC18) and the effect on cell viability (Trypan blue) and apoptosis (Acridine orange) measured. Non-inflamed colonic mucosal explants were also incubated with NOC18 and apoptosis measured by morphological techniques following staining with haematoxylin and eosin. Negative controls were performed with culture medium alone and decomposed NOC18. Peroxynitrite formation was also inhibited by co-incubation with superoxide dismutase (SOD) and catalase (CAT).

Results: In HT29 cells, NOC18 reduced cell viability (LD_{50} 12 mM compared with medium alone). This effect was not seen with either decomposed NOC18 (DETA) or co-incubation with SOD and CAT. A significant increase in colonic epithelial cell apoptosis was also seen in mucosal explants incubated with 1 mM NOC18 ($p=0.033$) compared to medium alone which was not seen with DETA.A similar increase in apoptosis was also seen in HT29 cells with 1 mM NOC18 ($p=0.012$) compared with medium alone which was not seen with DETA but was abolished when co-incubated with SOD and CAT.

Discussion: Supraphysiological concentrations of NO results in both necrosis and apoptosis of colonic epithelial cells. Neither of these effects occurs with decomposed NOC18, suggesting that neither the carrier molecule nor stable by products of NO degradation are important. Although a direct effect of NO seems to be important in necrotic cell death, peroxynitrite appears to be play a role in NO induced apoptosis as this effect was abolished with SOD and CAT. NO mediated necrosis and apoptosis of colonic epithelial cells may play a role in active inflammation in ulcerative colitis by reducing epithelial barrier function and increasing contact between luminal factors, such as colonic bacteria and the mucosal immune system.

382 MANAGEMENT OF LOW AND HIGH GRADE DYSPLASIA IN INFLAMMATORY BOWEL DISEASE: A GASTROENTEROLOGIST'S PERSPECTIVE AND CURRENT PRACTICE IN UK

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Background: Colonic dysplasia is a precursor to colorectal cancer (CRC) in inflammatory bowel disease (IBD). There is a risk of progression of low and high grade dysplasia (LGD and HGD) to CRC over 5 years. The current BSG guidelines advocate colectomy when possible or *at least* 6 monthly surveillance.

Aim: To get an overview of the gastroenterologist's perspective on various aspects of colonic dysplasia in IBD and to see the current management practice in UK.

Methods: A national postal survey of 502 gastroenterologists listed in the BSG handbook 2003.

Results: 51% of questionnaires were returned. 30% did not consider LGD to be premalignant whereas all considered HGD to be so. Only 13% offered routine colectomy for LGD compared with 84% for HGD. More than a third felt that flat LGD might not have concurrent CRC, of which 95% did surveillance colonoscopies in this group. Only a small proportion of the remaining gastroenterologists treated flat LGD surgically (14%). On the other hand 85% considered LGD with dysplasia associated lesion or mass (DALM) constituted a high risk of concurrent CRC. Only 53% offered total colectomy to this group. There was a wide variation in the frequency of surveillance for LGD in flat mucosa and DALM. A majority agreed that LGD progressed to HGD (82%) and CRC (75%). However their perception of the risk of progression to either HGD or CRC over 5 years varied widely. All agreed that HGD may have coexistent CRC and 98% thought it progressed to CRC. Patients were more likely to be treated with colectomy for flat HGD (77%) and HGD with DALM (86%). 38% of the gastroenterologists felt that there was a more than 30% chance of having coexistent CRC in HGD of which 11% continued to manage them conservatively.

Conclusion: There are wide variations in the perceptions and management of LGD in IBD in UK compared to HGD where there seems to be a more uniform agreement. The need for more research in this area and a national agreement on management is paramount. Until this is reached gastroenterologists will remain open to criticism and litigation.

383 ACTIVATION OF CIRCULATING NEUTROPHILS (SHEDDING OF L-SELECTIN) IS INCREASED IN SMOKERS WITH CROHN'S DISEASE

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Background: L-selectin is shed by activated neutrophils. Smoking adversely affects the natural history of Crohn's disease (CD) although the pathogenic mechanisms involved are unclear. Although smoking acutely causes platelet activation and platelet-leucocyte aggregation, both of which are increased in IBD, its chronic effects on neutrophil activation are unclear.

Aims: To discover whether neutrophil activation, platelet activation, and platelet-leucocyte aggregation are increased in smokers with CD.

Methods: Whole blood flow cytometry was performed on samples taken from 31 patients with CD, 11 of whom smoked. Samples were incubated with fluorescent antibodies to CD62P (P-selectin–platelet activation), CD45 and CD42a (for platelet-leucocyte aggregates), and CD62L (L-selectin–neutrophil activation), and were analysed within 30 minutes (for in vivo activation) and at 180 minutes (for ex vivo spontaneous activation).

Results: The mean fluorescence intensity (MFI) of L-selectin on neutrophils was lower in smokers with CD than in non smokers, at both time points ($t=0$ smokers MFI = 793 (774–797), non-smokers 810 (789–819) $p<0.05$; $t=180$ smokers 784 (766–795), non-smokers 806 (781–819) $p<0.05$). There was no difference in the expression of P-selectin by platelets, or in the number of platelet-leucocyte aggregates between smokers and non-smokers. In addition, the ESR, CRP, and activity index scores (Harvey Bradshaw) were similar in both groups.

Conclusions: Patients with Crohn's disease who smoke have increased neutrophil activation, both in vivo and ex vivo, compared with those who do not smoke. This may contribute to the adverse influence of smoking on the prognosis of Crohn's disease.

384 SOCIAL DEPRIVATION AND MORTALITY IN INFLAMMATORY BOWEL DISEASE

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Background: Social deprivation associates with increased mortality in conditions such as colon cancer, heart disease, and diabetes. However its effect on mortality in inflammatory bowel disease (IBD) is not known.

Methods: All patients IBD attending since 1996 have been logged onto a centralised database. Townsend Deprivation Index was derived from postal code and allocated to quartiles according to pre-existing data for the Merseyside population.

Results: 914 patients with ulcerative colitis and 553 with Crohn's disease were identified. Between January 1996 and June 2002 there were 38 deaths in patients with ulcerative colitis and 35 deaths in patients with Crohn's disease.

Taking IBD as whole, the relative risk for overall mortality in the most deprived 50% was 2.07 (95% CI 1.21 to 3.56, p = 0.01) compared with that for the least deprived 50%.

For disease associated mortality see table 2.

Taking IBD as a whole, the relative risk for disease associated mortality in the most deprived 50% was 5.64 (95% CI 1.47 to 21.69, p = 0.02) compared with those in the least deprived 50%.

Conclusion: Disease associated mortality in IBD, even more than overall mortality, is associated with social deprivation, presumably because of poorer access to health care.

Abstract 384, table 1

Overall mortality by deprivation quartile	Most deprived	Second quartile	Third quartile	Least deprived
Ulcerative colitis	28/495	2/75	8/274	0/74
Crohn's disease	25/336	2/34	8/152	0/31

Abstract 384, table 2

Disease associated mortality by deprivation quartile	Most deprived	Second quartile	Third quartile	Least deprived
Ulcerative colitis	8/495	0/75	1/274	0/74
Crohn's disease	11/336	1/34	2/152	0/31

385 FUNCTIONAL SYMPTOMS IN INFLAMMATORY BOWEL DISEASE

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Introduction: Functional symptoms seem common in inflammatory bowel disease (IBD), putting patients at risk of mismanagement. There is little existing literature, but one study suggested a prevalence of 33% in ulcerative colitis (UC) and 57% in Crohn's disease (CD); higher than that in the general population.[1]

Aims and Methods: We attempted to assess functional symptoms across the IBD spectrum in comparison with patients with irritable bowel syndrome (IBS). Each participant completed a questionnaire addressing bowel habits, abdominal pain, functional symptoms, and general wellbeing. Scores for three IBD activity indices and two IBS indices were calculated for each patient.

Results: 190 patients completed questionnaires: 76 with CD, 88 with UC, and 26 with IBS. The groups scored similarly on the IBD indices and 62% of the IBS cohort had mCDAI scores >150. CD patients reported apparent functional symptoms at similar levels to IBS patients. UC patients had fewer functional symptoms.

Conclusion: Existing disease indices lack power to distinguish between functional and organic symptoms. It is not possible to be confident about the prevalence of functional symptoms in IBD. However, this is the first study to compare symptoms in IBD and IBS patients and to examine functional symptoms across the IBD spectrum. IBD patients (especially those with CD) seem to have comparable rates of functional symptoms to those with IBS

1. **Simren M**, *et al*. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;**97**:389–96.

386 A NOVEL INDEX TO ASSESS FUNCTIONAL SYMPTOMS IN INFLAMMATORY BOWEL DISEASE

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Introduction: Functional symptoms occur in inflammatory bowel disease (IBD) probably more than in the general population. Existing disease indices lack objectivity, relying in part on the functional symptoms that overlap with organic disease manifestations.

Aims and Methods: Our aim was to devise a structured evaluation of functional symptoms in IBD. Patients with Crohn's disease (CD), ulcerative colitis (UC), or irritable bowel syndrome (IBS) completed symptom questionnaires to generate 3 IBD activity indices and an IBS index. Outliers (high functional but low organic scores) were chosen as exemplars from whom to devise a new index.

Results: 190 patients returned questionnaires: 76 had CD, 88 UC, and 26 IBS. Nine IBD patients had high IBS scores (>70th centile) but low IBD scores (<30th centile); key features included bloating, wind, and severe fatigue, and the absence of diarrhoea and nocturnal symptoms. A new (0–30) scoring system was devised, including 8 questions evaluating a spectrum of both functional and ''anti-functional'' symptoms. Prospective evaluation in a separate cohort of 76 IBD patients yielded scores from 0–21. The scores correlate poorly with IBD indices, inflammatory markers, and formal psychometric scores. This is logical and appears to satisfy our aim, seeking patients who score highly but are psychologically well adjusted, with evidence such as low inflammatory markers suggesting that their symptoms are not solely organic. Novel, useful information is being acquired.

Conclusion: The identification and management of functional symptoms in IBD remain clinical problems. The new index needs further validation, but appears a potentially important step forwards.

387 TPMT GENOTYPE: IS THIS A COST EFFECTIVE ASSAY FOR PATIENTS ABOUT TO BEGIN AZATHIOPRINE TREATMENT FOR INFLAMMATORY BOWEL DISEASE?

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Introduction: Azathioprine is an extremely useful drug for the treatment of relapsing inflammatory bowel disease (IBD). Adverse reactions occur in 15% of which the most dangerous is myelosuppression. This is usually an early event, unpredictable, and seen in 3.2% of patients. It poses a mortality risk. Current practice is to monitor the blood count regularly to detect marrow toxicity at an early enough stage to stop therapy and avoid life threatening sepsis. Deficiency of the hepatic enzyme thiopurine methyltransferase (TPMT) is responsible for a proportion of cases of myelosuppression. Assay of white blood cell TPMT gene polymorphisms allow identification of patients who are homozygous (0.3%) or heterozygous (11%) for alleles predicting low TPMT enzyme levels. However, the clinical utility of these assays has not been established.

Aim: The aim of this study was to evaluate the cost effectiveness of screening for TPMT gene polymorphisms before initiation of azathioprine treatment.

Methods: Analysis of the literature was undertaken to calculate the expected frequency of side effects and resulting costs of treatment in a theoretical 1000 IBD patient population who were initiated on azathioprine treatment. Decision analysis was applied to assess the relative costs of two monitoring strategies (regular blood monitoring ± TPMT genotyping) to determine direct costs and cost per life year saved.

Results: The net additional cost of screening 1000 patients for TPMT polymorphisms is £37 136. Using the most conservative estimates, based on avoiding one death, the cost per life year saved is £790 for a thirty year old and £1857 for a sixty year old.

Conclusion: The use of pretreatment screening for TPMT polymorphisms in IBD patients starting azathioprine treatment represents good value for money.

388 EOSINOPHILS LOCALISE TO NERVES IN PATIENTS WITH IBD THROUGH SPECIFIC NEURALLY EXPRESSED ADHESION MOLECULES AND CHEMOATTRACTANTS

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Introduction: The role of the eosinophil, which is a common inflammatory cell in inflamed gastrointestinal mucosa in inflammatory bowel disease (IBD) is uncertain. We have previously shown that eosinophils specifically localise to nerves in patients with IBD. The aim of this study was to define the mechanism of this localisation.

Methods: Using formalin fixed paraffin embedded tissue from patients who had previously undergone colonic resection for intractable IBD, the mechanisms of recruitment to enteric nerves were assessed. Paraffin embedded tissue was stained for nerves using S100, then dissected using Arcturus laser capture micro-dissection system. The RNA was reverse transcribed and the cDNA amplified using TAQ and specific primers for ICAM-1 and eotaxin-3.

Results: Compared with controls (n = 5), ICAM-1 was increased sevenfold in patients with ulcerative colitis (n = 4), (p = 0.03), and 10-fold in those with Crohn's disease (n = 3), (p = 0.05). Eotaxin-3 was increased ninefold in the patients with ulcerative colitis (p = 0.04) and 15-fold in those with Crohn's disease (p = 0.06) compared with controls.

Conclusions: Specific neurally expressed adhesion molecules and a specific eosinophil chemoattractant appear to mediate localisation of eosinophils to nerves. The significance of these specific neuro-immunological interactions will require further investigation. Neurally mediated eosinophil chemoattractants may contribute to the inflammatory cascade in IBD.

389 EOSINOPHILS DISPLAY AN ACTIVATED PHENOTYPE IN CLINICALLY ACTIVE INFLAMMATORY BOWEL DISEASE

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Introduction: The role of the eosinophil, which is a common inflammatory cell in inflamed gastrointestinal mucosa in inflammatory bowel disease (IBD) is uncertain. Eosinophils may lead to symptoms through the release of toxic cationic proteins, or contribute to remodelling through the release of TGF-β.

Aim: The aim of this study was to evaluate the phenotype of eosinophils in large bowel mucosa of patients with (1) symptomatic active disease that was responsive to treatment (n = 6), (2) subjects refractory to treatment (n = 15) and (3) control non-affected subjects (n = 10). Eosinophil numbers, release of cationic major basic protein (MBP), and expression of TGF-β were determined.

Methods: Formalin fixed, paraffin embedded tissue from these patient groups was studied. Eosinophils were identified using a polyclonal anti-rabbit antibody to eosinophil MBP followed by detection using a peroxidase linked chromagen. The use of this antibody to MBP allowed intact, as well as degranulating eosinophils to be identified. TGF-β was detected using a mouse antihuman monoclonal antibody and sections were counterstained with haemotoxylin to identify eosinophils.

Results: The number of eosinophils was significantly increased in patients with ulcerative colitis (UC) and Crohn's disease (CD) compared with controls. Release of extracellular MBP was seen most markedly in active UC and to a lesser extent in CD before corticosteroid treatment. In contrast, in corticosteroid refractory IBD, while there was a considerable increase in the number of eosinophils, there was no release of MBP and only a small proportion of these cells (1%) were TGF-β positive.

Conclusion: Significant eosinophil accumulation is seen in IBD. Degranulation rates vary with disease activity. A potential therapeutic role of eosinophil inhibition remains to be explored.

390 DOES HEPARIN RESTORE EPITHELIAL GAG EXPRESSION IN INFLAMMATORY BOWEL DISEASE?

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Background: Recent trials that have looked at the efficacy of low molecular weight heparins (LMWH) in ulcerative colitis (UC) have found no benefit over placebo, which is in contrast to earlier trials with unfractionated heparin where high rates of remission were seen. One of the proposed mechanisms of heparin treatment is that it acts as a co-receptor for basic fibroblast growth factor (bFGF), which is important in healing of ulceration. This function is usually performed by mucosal glycosaminoglycans (GAGs), which are depleted in the ulcerated mucosa of patients with inflammatory bowel disease (IBD).

Aim: To examine whether heparin therapy restores loss of GAG expression in the mucosa of UC patients.

Methods: Rectal biopsies were taken from a subset of patients with active ulcerative colitis from a multicentre placebo controlled trial of Innohep, a LMWH. Patients were randomised to receive either Innohep or placebo for six weeks, and rectal biopsies were taken before and after the course of treatment. Rectal biopsies were also obtained from patients with active UC who were treated with open label unfractionated heparin. Six paired biopsies were available where samples were taken before and after treatment; unfractionated heparin (2), Innohep (1), placebo (3). Histochemical staining of the tissue sections was used to visualise GAGs using a 5 nm gold-conjugated poly-L-lysine probe and silver enhancer. Crypt and surface epithelium were both allocated scores for intensity of membrane staining at a final magnification ×250 by two independent observers unaware of the treatment category (strong (3), reduced (<50%) (2), or negative staining (1)). Four randomly selected areas in each biopsy containing both crypt and surface epithelium were scored and the averages calculated.

Results: The change in score after treatment for each group is shown below. The patient who received Innohep had increased GAG staining post-treatment whereas the two patients who received UH had an average decrease in surface epithelium GAG staining. The three patients who received placebo showed minimal change.

Discussion: Although unfractionated heparin and LMWH have comparable anticoagulant properties, their effects on epithelial GAG expression seem to differ to a major extent. This may be key in UC.

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Group	Change in score for surface epithelium	Change in score for crypt epithelium
Unfractionated heparin	−1.5	0
LMWH	+1.5	+1
Placebo	−0.1	+0.5

391 QUALITY OF CARE FOR OUTPATIENTS WITH IBD: DOES IT MATTER WHERE THEY ARE SEEN?

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Introduction: Long term follow up of patients with inflammatory bowel disease (IBD) is rarely critically audited. At this Trust, IBD patients are reviewed either in one of 3 general gastroenterology clinics (GGC), or in a specialist IBD clinic (IBDC) attended by a pharmacist, dietician, and informal counsellor in addition to medical staff.

Aim: To compare quality of care of patients with IBD in specialist IBDC and GGC using defined criteria.

Methods: A standard proforma was completed after the clinic visit for 121 consecutive IBD patients attending the IBDC (n = 83) or the GGCs (n = 38). The following quality criteria were assessed for the preceding eighteen months: biweekly FBC and LFT monitoring for two months during initiation phase and every three months thereafter for patients on thiopurines; co-prescription of bone protective treatment with oral prednisolone; colonoscopy for patients with ulcerative colitis at 8–10 years; annual LFTs; annual urea and creatinine for patients on aminosalicylates; and annual haematinics for patients with Crohn's.

Results: see table.

Conclusions: Using these criteria, even in a specialist IBD clinic, a substantial minority of patients receive suboptimal monitoring and treatment. The results in general gastroenterology clinics, often attended by the same doctors, were significantly worse and suggest that patients with IBD would fare better in a specialist setting.

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Patients fulfilling criteria	IBDC (%)	GGC (%)	p Value
Azathioprine initiation testing	7/11 (64)	2/8 (25)	0.17
Azathioprine maintenance testing	20/28 (71)	2/11 (18)	0.004
Bone protection with steroids	26/52 (50)	3/25 (12)	0.001
Colonoscopy at 8–10 years	23/25 (92)	7/11 (64)	0.057
Annual LFTs	73/76 (96)	28/37 (76)	0.002
Annual U+E for 5-ASA	63/69 (91)	23/31 (74)	0.031
Annual haematinics for Crohn's	30/32 (94)	17/28 (61)	0.004

392 DIRECT COSTS OF ACUTE FLARES OF INFLAMMATORY BOWEL DISEASE

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Introduction: Availability of cost data for IBD is limited for the UK, owing to a single payer provider healthcare system in which patient specific costing information is not collected routinely.

Aims and Methods: We aimed to compare direct costs associated with an acute flare of ulcerative colitis and Crohn's disease (CD) with routine care costs for quiescent UC and CD. Patients receiving any form of care for IBD at our centre (a university hospital serving 333 000 inhabitants) over a 6 month period were identified and information relating to resource use abstracted. Unit costs were derived from local/national sources.

Definitions: Quiescent disease: no change in disease severity or drug treatment during the study period, not requiring immunosuppressants or any specialist investigation during the study period. Disease ''flare'': transition from mild disease (no treatment; 5-ASA maintenance; or topical treatment only) to more severe disease needing immunosuppressant.

Results: 479 IBD patients received care over the study period (median (IQR) cost/patient/6 months: UC £506 (314–787) and CD £507 (271–946)), with 245 fulfilling criteria for study entry (either quiescent disease or a disease flare): quiescent UC, n=117; flare of UC, n=43; stable CD, n=55; flare of CD, n=30. No significant differences between demographics or disease extent for quiescent *v* flare patients for either form of IBD. Median (IQR) of cost/patient/6 months: quiescent UC £346 (£162–469) *v* flare of UC £819 (£619–2345), $p<0.001$. Quiescent CD £265 (£126–370) *v* flare of CD £1771 (£681–3874), $p<0.001$. Median (IQR) of cost/patient/6 months of those needing inpatient management of acute flare *v* those whose flare was managed as an outpatient: hospitalised UC: £5540 (3653–12293) *v* ambulatory UC £693 (540–829); hospitalised CD £3677 (£3069–7769) *v* ambulatory CD £648 (£313–764)

Conclusion: The management of stable IBD is associated with significant health care costs but disease flares are accompanied by a two- to threefold increase in 6 month secondary care costs. Strategies to maintain remission, such as measures to improve compliance with maintenance 5-ASAs in stable UC, may limit healthcare costs while maximising quality of life.

393 AN AUDIT OF GUIDED PRIMARY CARE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE IN A DISTRICT GENERAL HOSPITAL

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Background: Inflammatory bowel disease (IBD) is usually managed by gastroenterologists in secondary care. Patients with IBD in clinical remission often are reviewed regularly in the outpatient department (OPD) using 15 million appointments each year in the UK. Alternatively, patients and GPs may be given information about monitoring drug side effects and treatment of relapses with the opportunity of OPD review $\leqslant 2$ weeks guided primary care management (GPCM). This style of IBD management was started in 1997.

Aim: To determine if GPCM is an acceptable and safe way of managing stable IBD and whether it decreases the need for routine OPD follow up.

Methods: Patients who were discharged from OPD with GPCM >6 months earlier (range 7–32; mean 17 months) were randomly selected from secretarial OPD files. Telephone interviews were conducted by JSF and EDT who asked about number and treatment of any relapses, need for consultant review and time taken for OPD appointment.

Results: 51 patients (23 female) aged 16–85 (mean 48) years were interviewed; 35% with Crohn's disease, 43% with distal ulcerative colitis or proctitis, and 22% with extensive or pancolitis. 22% of patients were taking azathioprine or 6-mercaptopurine. 30 (59%), 18 (35%), and 3 (6%) of patients had no relapse, one relapse, or >1 relapse since OPD discharge, respectively. Nine of the relapses were treated by GP alone. 13 patients required further OPD review; 8 requested appointment via AWH secretary and all were seen <2 weeks. Five patients were re-referred by GP and 2 of these were seen <2 weeks. One patient was referred directly to A&E. There were no serious drug side effects, operations, or deaths. No patient was referred to another gastroenterologist.

Conclusions: GPCM of IBD in this population appears to be acceptable and safe (including patients on immunosuppression). 13 follow up appointments were requested by patients or GPs compared with the expected number of 126 (one every 6 months/patient) resulting in a net gain in OPD capacity of 113 follow up appointments.

394 INFLIXIMAB USAGE FOR CROHN'S DISEASE: A WEST MIDLANDS SURVEY

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Background: Infliximab, a chimeric monoclonal anti-TNF-α antibody, was licensed for usage in Crohn's disease in the UK in 1999, and was believed to represent a major advance in therapeutic options. However there remain few data on medium to long term follow up on patients treated with Infliximab.

Aims and Methods: We reviewed usage of Infliximab and clinicians' evaluation of its efficacy. Questionnaires were mailed to 48 consultant gastroenterologists in the West Midlands. To allow for clinical follow up, data were restricted to patients treated before the NICE guidelines (April 2002).

Results: 45 consultants (94%) responded. Of these, 27 (60%) have used Infliximab in a total of 59 patients. Detailed information has been gathered for 30 patients. The male:female ratio was 11:19 and median age 28 (IQR 23–40). All 30 patients had chronic active Crohn's disease, with 13 patients having fistulating disease. 24 patients (80%) had previously taken one or more immunmodulatory agents—azathioprine (n=22), 6-MP (5), methotrexate (4), or cyclosporin (4). The median number of Inliximab infusions per patient was 3 (interquartile range 2–5). After a median of 20 months since commencing infliximab, 8 patients required surgery, and 4 required 9 or more Infliximab infusions to maintain remission. In 24 patients (80%), the clinician considered Infliximab to have initially significantly improved their condition. This improvement was sustained in 18 of these patients. Most patients were funded on a case by case basis (n=23), with only one consultant prescribing freely.

Conclusions: Only around half of West Midlands' gastroenterologists reported usage of Infliximab prior to NICE guidelines. Some patients had sustained benefit but a proportion still required surgery, others required multiple infusions. Further follow up and surveillance may clarify its clinical and health economic impact.

395 AZATHIOPRINE REDUCES RELAPSE RATE IN CROHN'S DISEASE PATIENTS IN STEROID INDUCED CLINICAL REMISSION BUT WITH ELEVATED FAECAL CALPROTECTIN

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Background: Several surrogate markers of mucosal inflammation have been shown by us and others to be useful in predicting relapse after clinical remission induced by corticosteroids in Crohn's disease (CD). These include intestinal permeability, mucosal concentration of TNF and IL-1β, whole gut lavage cytokines IL-1β and IL-8, and faecal calprotectin.

Aim: To demonstrate if early immunosuppressive treatment in CD patients in clinical remission but at high risk of relapse (shown by evidence of subtle mucosal inflammation such as higher faecal calprotectin levels) can reduce the relapse rate in the subsequent 12 months.

Patients and Methods: A total of 67 CD patients were considered to be in clinical remission (CDAI <150) at 8 weeks after commencement of prednisolone starting at a dose of 40 mg/day (including budesonide 9 mg/day, n=13). A total of 46 patients were considered to be at high risk of relapse by virtue of having a high faecal calprotectin concentration (>50 μg/gm). 24 patients received azathioprine (2 mg/kg body weight) and mesalazine (Asacol) 2.4 g per day, and 22 patients received mesalazine (Asacol) 2.4 g per day. The patients were followed up for 12 months and results were analysed on an intention to treat basis using Kaplan Meier survival analysis. The two groups of patients were well matched regarding their disease duration, baseline CDAI, proportion of smokers, and mean dose of prednisolone at baseline.

Results: At 52 weeks after randomisation, 16/24 patients (66%) in the azathioprine plus mesalazine arm of the study had discontinued corticosteroids, compared with 7/22 (31%) in the mesalazine alone arm ($p<0.02$). The time to relapse and percentage of patients in remission over 1 year was significantly higher in those treated with azathioprine plus mesalazine compared with those treated with mesalazine alone (log rank test $\chi^2=4.67$; $p=0.03$; relative risk 0.4).

Three patients in the azathioprine arm had discontinued the medication during the study period (due to neutropenia, skin rashes, and pancreatitis).

Conclusion: High risk of relapse in those with elevated faecal calprotectin after medical induction of remission in Crohn's disease may be significantly attenuated by treatment with azathioprine over a one year period (with concurrent mesalazine) compared with mesalazine alone. This study provides support for the use of faecal calprotectin as a therapeutic endpoint.

396 INCREASED EXPRESSION OF HEME-OXYGENASE 1 IN INFLAMMATORY BOWEL DISEASE, COLORECTAL CANCER, AND BARRETT'S OESOPHAGUS

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Introduction: Heme-oxygenase (HO) is the rate limiting enzyme in the metabolism of heme to form biliverdin, carbon monoxide, and free iron. It has an inducible form HO-1 and a constitutive form HO-2. HO-1 is highly conserved and essential for life. It has been suggested that in addition to heme metabolism HO-1 may have an anti-oxidant and anti-inflammatory role. Induction of HO-1 in pulmonary, hepatic, and brain tissue has been shown to reduce tissue damage under ischaemic and inflammatory conditions.

Aim and Methods: Using immunohistochemistry techniques a comparison was made between the distribution of HO-1 and HO-2 in normal colonic tissue (22 cases), inflammatory bowel disease (22 cases), colorectal cancer (17 cases), normal oesophageal tissue (20 cases), and Barrett's oesophagus (20 cases). Controls for each case were performed by omitting the primary antibody. Staining intensity was rated on a 3 point scale to aid comparison (0, 1, 2).

Results: HO-1 was present in the cytoplasm of epithelial cells, macrophages in the lamina propria, endothelial cells of blood vessels, and ganglion cells. A similar distribution was also found for HO-2. HO-1 staining intensity was increased in the epithelial cells in IBD (average score = 1.85), colorectal cancer (1.85) compared with normal colon (1.62). Barrett's oesophagus epithelial staining was increased (1.82) when compared to normal oesophagus (1.6).

Conclusions: HO-1 and HO-2 are expressed in normal colonic and oesophageal epithelium. HO-1 expression is increased in IBD, colorectal cancer, and Barrett's oesophagus, which may represent a physiological response to oxidant stress in these conditions.

397 A PATIENT CENTRED APPROACH TO MEASURING THE IMPACT OF FAECAL INCONTINENCE IN IBD

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We report on the development and preliminary validation of a new scale to measure the impact of faecal incontinence (FI) in patients with inflammatory bowel disease (IBD). FI has been defined as the involuntary or inappropriate passage of faeces. Here we have used a broader definition to include anal incontinence. There is a misconception that FI results only from neurological disorders or obstetric trauma. However, FI is a significant feature of IBD, highlighted in studies of rectal pathophysiology, yet it is underreported by patients and rarely asked about by clinicians. We adopted a patient centred, multi-method approach. 553 IBD patients responded to a postal survey to assess the prevalence and severity of FI. Results indicate 87% of respondents had experienced FI in adulthood and 71% had experienced FI in the 4 weeks up to completion of the questionnaire. A purposive sample took part in in-depth and semi-structured interviews designed to inform the understanding of the fears and concerns of living with FI and the impact of the condition upon life and lifestyle. Emergent themes were drafted into questionnaire items which were rated by participants (n = 79) for applicability and importance. Following initial item reduction, factor analysis yielded a unitary 36 item scale. Due to poor face validity one item was removed from the final scale. Cronbach's alpha = 0.97 suggested redundancy and a shorter 18 item scale (face validity being the selection criterion) was constructed (Cronbach's alpha = 0.96). The test-retest reliability coefficient for the 35 and 18 item scales was 0.93 and 0.91 respectively suggesting a high level of stability over time. Further analyses show a strong positive correlation between the QoLiFI scale, severity and frequency of FI, lifestyle alteration due to FI, and worry about FI. Existing scales—for example, HADS—produce similar moderate to good correlations with the QoLiFI items.

398 EFFECT OF NICOTINE ON IL2 AND HUMAN β-DEFENSIN 2 (HBD2) RESPONSES IN AN ORGAN CULTURE MODEL IN IBD

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Introduction: The effects of smoking in inflammatory bowel disease (IBD) are now well established, but the mechanisms by which these occur are unknown, affecting innate or acquired immune responses. Defensins are small molecules produced by epithelial cells, which are thought to have some role in innate defence to micro-organisms.

Methods: We used an organ culture method to incubate colonic biopsies from patients with CD (n = 6), UC (n = 4), and controls (HC, n = 12) with differing concentrations of nicotine, LPS, and LPS+nicotine. IL2 and human β defensin 2 (HBD2) were measured in culture supernatants by ELISA.

Results: Production of IL2 was highest in basal and LPS stimulated biopsies from HC compared with CD or UC ($p = 0.0463$, two way ANOVA), although comparison of each stimulant in turn was not significant. HBD2 was highest in basal and LPS stimulated biopsies from UC patients compared with HC or CD ($p < 0.0139$, two way ANOVA). There was no consistent pattern of IL2 production in response to nicotine alone in any disease group. However, on comparison of biopsies stimulated with LPS alone and LPS+nicotine from the same patients, an increase of >50 pg/ml in IL2 production was seen in 5/5 CD, but only 1/4 UC and 4/11 HC ($\chi^2 = 6.818$, $p = 0.033$). For HBD2, there was little change in response to any stimulant.

Discussion: IL2 production is reduced in CD and UC compared with HC, whereas HBD2 is significantly increased in UC. Neither IL2 nor HBD2 levels significantly changed in response to nicotine alone at any concentration, nor did HBD2 change in response to LPS, with or without nicotine. However, IL2 production was increased in CD when nicotine was combined with LPS, whereas it decreased in UC and HC. These changes in IL2 production may be enough to offset the finely tuned local inflammatory responses in the gut, and explain disease differences in response to smoking.

399 PREDICTING THE RATE OF BONE LOSS IN CROHN'S DISEASE USING BIOCHEMICAL MARKERS OF BONE TURNOVER

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Background and Aims: Identification of patients with Crohn's disease (CD) at greatest risk of rapid future bone loss would be an important advance in targeting treatment in this group at high risk of osteoporosis. In postmenopausal women, biochemical markers of bone turnover effectively identify ''fast'' and ''slow'' losers of bone and can predict future hip fractures.

The aim of this study was to prospectively evaluate the predictive value of bone turnover markers in patients with CD.

Patients and Methods: Bone mineral density was measured at the femoral neck and lumbar spine by dual energy *x* ray absorptiometry scan (DEXA) at baseline and after 12 months in 54 patients (21 = male, mean age = 40.9 years) with CD. At baseline, Osteocalcin (BGP), bone specific alkaline phosphatase (BALP), and pro-carboxyterminal propeptide (PICP) were measured to assess bone formation; urinary deoxypyridinoline (DPD) was measured to assess bone resorption. Bivariate correlation and independent *t* tests were applied to evaluate the predictive value of bone turnover markers.

Results: Mean % change in BMD at the spine was +0.76 (SD 3.21) and 0.55 (SD 3.52) in the neck. 14 (26%) patients lost more than 5% of BMD in one or more sites. There was no significant difference in the amount of bone loss with respect to sex, age, nutritional status, smoking or alcohol history, disease activity, steroid usage, previous bowel resection, or previous history of fractures. Baseline levels of bone turnover markers were not significantly associated with change in BMD at the hip (BGP ($r = 0.06$), BALP ($r = 0.22$), PICP($r = -0.08$), DPD ($r = 0.07$) or spine (BGP ($r = 0.07$), BALP ($r = 0.17$), PICP ($r = 0.22$), DPD ($r = -0.13$). In the 14 patients with higher rate of bone loss, none of the bone turnover markers could predict this change either.

Conclusions: A significant proportion of patients with CD experienced high rates of bone loss. Baseline levels of bone turnover markers were not significantly associated with change in BMD in the whole group or in

''fast'' losers. Biochemical markers will therefore, not be useful in identifying individuals at greatest risk of rapid bone loss.

400 *CLOSTRIDIUM DIFFICILE* AND ULCERATIVE COLITIS: DOUBLE TROUBLE

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Background: *Clostridium difficile* has been implicated in the relapse of patients with ulcerative colitis (UC) in India (Kochhar, *et al. J Clin Gastro* 1993) but other studies have suggested no association. Moreover, the natural history of UC complicated by *C difficile* is not well known.

Aims: To determine the clinical course of UC patients co-infected with *C difficile*

Methods: Patients with UC relapse and coincident *C difficile* infection presenting during a 30 month period (January 2001–June 2003) were identified from the hospital and microbiology laboratory databases. Information regarding treatment and outcome was extracted from casenotes.

Results: Twenty six UC patients were identified with UC relapse complicated by stool positivity for *C difficile* toxin; 18 of these required admission with severe colitis (defined according to Truelove-Witts criteria). Only 13 patients (50%) had a history of recent (<3 months) antibiotic exposure. All patients requiring admission received systemic steroids, initially intravenous hydrocortisone 100 mg qds. Five (19% overall, 28% of severe patients) underwent colectomy; 1 died due to postoperative complications (overall mortality rate 3.8%) but the other 21 went into remission at a median of 4 weeks (range 2–16). Patients with UC and *C difficile* had unusually high serum CRP concentrations (median 41 mg/dl; range 5–285) and patients whose serum CRP was >45 mg/dl after 3 days of systemic steroid therapy only had a colectomy rate of 33% (see table).

Conclusions: Although *C difficile* infection, when appropriately treated, does not seem to worsen the outcome of UC, it is associated with increased serum CRP and the usual criteria for predicting colectomy (Travis, *et al. Gut* 1996) can no longer be reliably applied.

Abstract 400

	CRP>45 (n = 12)	CRP<45 (n = 14)
Median (range) to remission	5 weeks (2–16)	4 weeks (2–12)
30 day colectomy rate	33.3%	7.1%

401 A NOVEL METHOD TO INVESTIGATE THE INFLAMMATORY RESPONSE IN THE BOWEL, AND CONFIRMATION OF ITS IMPAIRMENT IN CROHN'S DISEASE

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Background: Crohn's disease has been associated with reduced ability to recruit neutrophils to sites of trauma. Investigation of this effect has previously been restricted to the skin, by creating inflammatory windows by dermal abrasion or raising cantharidin blisters.

Aim: We set out to determine the relevance of these findings to the gastrointestinal tract, where most Crohn's lesions manifest.

Method: Two rectal biopsies were taken, to trigger an inflammatory reaction and to act as baseline samples. Subsequent biopsies were taken at 6 h from a site immediately overlying the initial biopsy (always directly identified sigmoidoscopically). The accumulation of neutrophils, determined by immunohistochemical staining of myeloperoxidase, and production of interleukin-8 were scored using a visual analogue scale (VAS) between 0–10, by two gastrointestinal pathologists, who were blinded to the origin of each section.

Subjects: Six adult patients with Crohn's disease were compared to 8 controls, approximately matched for age, sex, and smoking history. No patient was taking immunosuppressive or anti-inflammatory medication. All had inactive disease (Harvey Bradshaw score <3).

Results: The baseline biopsies were similar in both groups and all within normal limits. Internally validated neutrophil influx and interleukin-8 production were consistently induced in the controls (VAS: 8.0, $p<0.0001$; and 6.4, $p<0.001$ respectively). In all Crohn's disease patients, the accumulation of neutrophils was significantly reduced compared to controls (VAS: 2.7, $p<0.01$) and interleukin-8 production was virtually absent (VAS: 0.25, $p<0.0005$). This was independent of disease location.

Conclusion: This work provides a new method to study acute inflammation in the gut, and adds considerable weight to the hypothesis that Crohn's disease actually represents a form of immunodeficiency.

402 CHANGES IN QUALITY OF LIFE AND COGNITIVE FUNCTION FOLLOWING IRON THERAPY TO TREAT ANAEMIA IN A POPULATION OF IBD PATIENTS IN A BRITISH DISTRICT GENERAL HOSPITAL

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Background and Aims: Anaemia commonly complicates inflammatory bowel disease (IBD).[1] In patients with chronic renal failure the treatment of anaemia with iron +/− erythropoietin improves both quality of life (QOL) and cognitive function (CF).[2–5] The same drugs are effective in treating severe anaemia in IBD but there is no evidence to direct treatment of mild anaemia.[6 7] Concern exists that the use of iron may exacerbate inflammation in patients with IBD.[8] This study aimed to assess if changes in haemoglobin (Hb) in a population of IBD patients were associated with changes in QOL and CF independent of changes in disease activity (DA). Subsidiary aims were to assess if the use of iron was associated with worsening DA.

Patients and Methods: A cohort of 51 patients with IBD (30 Crohn's and 21 UC) took part. Iron replacement was given to 22 patients with low Hb. Measures of QOL, CF, DA, and Hb recorded at baseline and at 6 months.

Results: The iron treated group had lower Hb and higher DA scores compared to the non-iron treated group at baseline. In a hierarchical regression model, changes in DA accounted for 28% ($p=0.007$), and changes in Hb accounted for 10% ($p=0.021$), of the variance in change in QOL. No statistically significant associations were identified between changes in Hb or DA and CF. The same number of flare ups were seen in both groups. The DA and Hb were similar in both groups at the end.

Conclusions: Improvements in Hb will improve QOL scores in IBD patients independent of changes in DA. We found no similar effect with CF. We found no evidence that iron treatment caused worsening of DA. We therefore advocate further research to investigate the optimal treatment of anaemia in the management of IBD, with specific studies designed to validate our finding that iron can be used safely.

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403 CHARACTERISATION OF THE DEFECT IN ACUTE INFLAMMATION IN CROHN'S DISEASE AND THE INFLUENCE OF CARD15

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Introduction: Crohn's disease is a chronic inflammatory disorder. Theories as to its causation focus on an over-activation of the immune response. Instead, we show that this disease is actually associated with a failure of acute inflammation.

Methods: Polymorphisms in the CARD15 gene increase susceptibility to Crohn's disease. The protein is expressed in mononuclear phagocytes, where it responds to muramyl dipeptide (MDP), a major constituent of bacterial cell walls. We investigated the acute inflammatory response in vivo using a modified skin window technique, and analysed the influence of CARD15 and MDP upon this process.

Results: Neutrophil accumulation was significantly reduced ($p<0.001$) in Crohn's disease patients, independent of CARD15 genotype. Release of early mediators of inflammation (such as histamine and eicosanoids) was normal, but there was a subsequent failure to induce chemotactic cytokines. Application of MDP to skin windows augmented this chemokine production in all subjects except patients carrying

CARD15 variants, and corrected neutrophil accumulation to normal levels in Crohn's patients who do not have CARD15 polymorphisms.

By examining gene expression (using DNA microarrays) and cytokine responses to MDP by macrophages from 8 healthy controls and 9 Crohn's patients with and without CARD15 polymorphisms, we found that induction of these chemokines was the principal role of CARD15.

Conclusions: We propose that Crohn's disease results from multiple lesions that impair the efficacy of initiating inflammation. CARD15 polymorphisms contribute to, but do not necessarily cause, this phenotype. Persistence of organic and bacterial matter in the bowel wall consequent to impaired immune clearance probably underlies granuloma formation, and chronic inflammation develops as a secondary phenomenon.

404 RESPONSES TO KININ AGONISTS IN NON-INFLAMED CAECAL MUCOSA FROM PATIENTS WITH ULCERATIVE COLITIS

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Background: Bradykinin B_1 receptors are inducible and synthesised de novo under conditions of inflammation or trauma and are likely to be involved in control and maintenance of inflammatory processes. In vitro study has shown the induction of B_1 receptors in damaged tissue. Upregulation of B_1 receptor expression in colonic mucosa taken from patients with active ulcerative colitis when compared with B_2 receptor expression has also been reported. These findings were most marked in actively inflamed tissue and raised but not significantly so in inactive UC.

Methods: Non-inflamed caecal biopsy samples from patients with UC (area 1.8 mm^2) were obtained and mounted in Ussing chambers. Tissues were voltage clamped using a World Precision Instruments Dual Channel Voltage Clamp and the short circuit current, (SCC) was continuously recorded using a MacLab 8e series and Power Macintosh computer in chart mode. Changes in short circuit current are presented as μAcm^{-2} and are given together with their standard errors. Epithelia were exposed to the B_1 receptor agonist, Des-Arg-Bradykinin (DAB), 10 μM, and subsequently to the B_2 receptor agonist Lys-Bradykinin (LBK), 1 μM, applied to the basolateral membrane.

Results: The basal SCC (BSCC) was 233.7 (SD 51.0) μAcm^{-2} (n = 10). LBK, 1 μM, produced a current increase of 54 (SD 11.9) μAcm^{-2}. No effect on SCC was seen with DAB alone (n = 7) but the effect of LBK, added after DAB was significantly potentiated (176 (SD 48) μAcm^{-2} n = 7, $p<0.01$).

Conclusion: The B_1 agonist DAB had no direct effect on the basal short circuit current in human colonic epithelial biopsies. LBK on the other hand resulted in a significant increase in presumed chloride secretion, via an effect on B_2 receptors. Pre-exposure to DAB significantly potentiated the responses to LBK.

405 CAN EARLY CRITERIA PREDICT THE NEED FOR SURGERY IN PATIENTS WITH ACUTE SEVERE COLITIS?

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Background: Despite widespread use of corticosteroids and adjunctive therapies in acute severe colitis, many patients will require colectomy during admission. A recent BSG survey estimated the national colectomy rate at 28%. Several studies have identified clinical and blood variables that predict the need for surgery; such criteria have not been reproduced consistently. Recent attention has focussed on predictive criteria from Travis *et al* (*Gut* 1996;**38**:905–10) whereby stools >8 or 3–8 with CRP >45 mg/l on day 3 of intensive therapy predicted 85% of colectomies.

Methods: We retrospectively analysed the notes of consecutive cases of acute severe ulcerative colitis, as defined by modified Truelove and Witts criteria, admitted to Addenbrooke's between June 2000 and December 2002. As well as admission and day 3 variables, data were collected on prior extent and duration of disease and use of steroids before admission. Single and multivariate analysis of the data were performed.

Results: Out of 48 admissions, 21 failed medical treatment (colectomy rate = 44%). Median time to colectomy was 11 days. Admission serum albumin <22 g/l was highly specific (96%) for colectomy, but sensitivity was low (38%). Similarly a dilated colon on *x* ray (defined by diameter ⩾6 cm) was specific (89%) but non-sensitive (43%) for colectomy. No individual or combination of variables, including the above, were both sensitive and specific for surgery. Patients positive for day 3 criteria from Travis *et al* (n = 30) had a 57% risk of colectomy and were more likely to require colectomy than those negative ($p<0.05$, Fisher's exact test). All patients who had a complete response (defined by Travis *et al* as stools <4 with no blood on day 7) remain free of surgery (n = 7).

Conclusions: A proportion of patients admitted with severe colitis could have been identified early as high risk for colectomy based on admission albumin <22 g/l or dilated colon on *x* ray. Travis' criteria on day 3 were not highly predictive of colectomy in this population but did have some discriminatory value. In acute severe colitis accurate prediction of colectomy remains difficult on simple criteria alone.

406 6-THIOGUANINE IS WELL TOLERATED AND REASONABLY EFFECTIVE IN CROHN'S DISEASE PATIENTS WHO ARE RESISTANT OR INTOLERANT OF AZATHIOPRINE AND METHOTREXATE

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Background: The management of patients with CD who have failed to respond or are intolerant to azathioprine and methotrexate remains challenging. Red blood cell 6-thioguaninenucleotide (6-TGN) levels correlate with drug efficacy and bone marrow suppression in patients treated with azathioprine. 6-thioguanine (6-TG) forms 6-TGN more directly and may therefore bypass some of the reasons for toxicity and lack of unresponsiveness to azathioprine.

Aim: The aim of the study was to investigate the efficacy and safety profile of 6-TG in CD patients.

Methods: 25 patients who were resistant (n = 20) or intolerant (n = 5) to azathioprine were treated with 20 (n = 16) or 40 (n = 9) mg of 6-TG once daily. All except 3 were also resistant (n = 14) or intolerant (n = 8) to methotrexate. FBC, LFT, adverse events and clinical activity were monitored monthly for at least 6 months. Clinical response was defined as withdrawal of infliximab or steroid or fistula improvement where appropriate. New episodes of steroid therapy, infliximab, surgery, or persistent elevation of Harvey-Bradshaw index above 7 during the first 6 months were considered as treatment failures.

Results: 22 of 25 patients (88%) were able to tolerate and continue the medications for at least 6 months. 6-TG was withdrawn in 2 patients because of nausea and vomiting and in 1 patient because of abnormal LFT which returned to normal upon stopping the medication (2 on 20 mg and 1 on 40 mg 6-TG). On an intention to treat analysis, 9 of 25 (36%) patients responded to treatment (6 of 16 (37.5%) patients on 20 mg and 3 of 9 (33.3%) patients on 40 mg of 6-TG).

Conclusion: In the short term, 6-TG is well tolerated and can be an effective alternative in CD patients who are resistant or intolerant to azathioprine and methotrexate. Recent reports of abnormal liver function with nodular hyperplasia are of concern but were not confirmed in this study over 6 months of treatment. However, larger controlled trials are warranted to further evaluate long term safety and efficacy of 6-TG before it can be added to standard treatment.

407 C677T AND A1298C METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) GENE POLYMORPHISM DOES NOT PREDICT TOXICITY OR EFFICACY OF METHOTREXATE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Background: Methotrexate (MTX) is increasingly being used in inflammatory bowel disease (IBD) patients who are resistant or intolerant of azathioprine. However the failure rate and incidence of side effects are both significant. MTX influences the activity of MTHFR, one of the enzymes in the folate pathway. Two MTHFR gene polymorphisms, C677T and A1298C, have been associated with reduced enzyme activity and studies in patients with rheumatoid arthritis have suggested an increase in adverse events associated with C677T polymorphism and possible increased efficacy with A1298C mutation.

Aims: The aim of the study was to determine whether MTHFR gene polymorphism can predict toxicity and efficacy of MTX in patients with IBD.

Methods: Bloods were obtained from 48 IBD patients who have been treated with MTX. C677T and A1298C MTHFR gene polymorphism was determined by using PCR. All patients were either receiving MTX or had discontinued MTX because of adverse events or lack of effect. The toxicity and efficacy of MTX were assessed and correlated with the C677T and A1298C polymorphism.

Results: Toxicity leading to withdrawal of MTX occurred in 5 of 23 (22%) wild type, 5 of 20 (25%) heterozygous, and 2 of 5 (40%) homozygous patients with C677T polymorphism (no significant differences).

Clinical efficacy of MTX was noted in 8 of 23 (35%) wild type, 7 of 20 (35%) heterozygous, and 2 of 5 (40%) homozygous patients with C677T polymorphism (no significant differences). Toxicity leading to withdrawal of MTX occurred in 6 of 17 (35%) wild type, 6 of 20 (30%) heterozygous, and 0 of 11 (0%) homozygous patients with C1298C polymorphism (no significant difference). Clinical response occurred in 7 of 17 (41%) wild type, 7 of 20 (35%) heterozygous, and 3 of 11 (27%) homozygous patients with C1298C polymorphism (no significant difference).

Conclusion: C677T and C1298C MTHFR gene polymorphism does not predict toxicity or efficacy of MTX in IBD patients.

408 PHARMACOGENETIC PROFILING IN AZATHIOPRINE TREATMENT: TPMT, ITPA, AND MTHFR POLYMORPHISMS AND TOXICITY

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Background: The activity of various of the enzymes affecting the metabolism of azathioprine are affected by allelic polymorphisms. Of these, thiopurine methyl transferase is the best known, but inosine triphosphate pyrophosphohydrolase (ITPA) and methylene tatrahydrofolate reductase (MTHFR) are also possible important influences influencing thioinosine triphosphate accumulation and methylation capacity respectively. The aim of this study was to examine the influence of TPMT, ITPA, and MTHFR polymorphisms on the incidence of toxicity on azathioprine.

Methods: 96 patients were studied who developed toxicity on azathioprine given for inflammatory bowel disease. TPMT deficiency was assessed phenotypically by tandem mass spectrometry, ITPA94C>A and MTHFR C677T polymorphisms by genotyping. A two sided Fisher's exact test was used to calculate relative risks of toxicity.

Results: As expected, TPMT deficiency was associated with toxicity (RR 2.0 (CI 1.5 to 3.0) p=0.005). The ITPA94C>A polymorphism was not associated with toxicity (RR 1.3 (CI 0.8 to 2.1) p=0.193). Interestingly, the MTHFR C677T polymorphism appeared protective against toxicity (RR 0.61 (CI 0.4 to 0.9) p=0.022).

Conclusions: Contrary to initial reports, ITPA deficiency does not appear to predict toxicity to azathioprine. TPMT deficiency is a strong predictor whereas the MTHFR C677T polymorphism, perhaps through limiting production of methylated metabolites, appears protective against toxicity.

409 PROSPECTIVE STUDY OF THIOGUANINE NUCLEOTIDE MEASUREMENT DURING AZATHIOPRINE TREATMENT FOR INFLAMMATORY BOWEL DISEASE

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Background: 6-thioguanine nucleotides (TGN) are considered to be the active cytotoxic metabolite of azathioprine (AZA) although the exact mechanism action of the drug is by no means understood. Response to AZA in inflammatory bowel disease (IBD) is variable and there has been considerable recent interest in whether dosing can be optimised according to levels of TGNs on treatment. However, data have been conflicting and no prospective study has been reported. The aim of this study was to assess the relationship between TGN levels and clinical response (CR) as part of a London IBD Forum prospective study of AZA for IBD.

Methods: Patients entering the study were treated with AZA at 2 mg/kg for at least 6 months. Blood for TGN level was taken at 4, 12, and 24 weeks. Clinical response was assessed by steroid withdrawal, fistula closure, and by HBI for Crohn's disease, Truelove & Witts score for ulcerative colitis. TGN levels were measured by HPLC assay and analysed against clinical response using a nonparametric test (Kruskal-Wallis).

Results: From 189 patients entering the study, there were 87 (59 CD, 28 UC, median age 38) who completed 6 months and in whom TGN data were available for analysis. Of these, complete response was achieved in 51/87 (58.6%). Although there was a trend toward higher TGN levels in those achieving clinical response to AZA, no significant relation could be determined (non-response: complete response p>0.05).

Conclusions: This prospective evaluation demonstrates that TGN levels are not a reliable enough guide to optimal dosing of AZA in IBD such that it is difficult to envisage their use in routine clinical practice.

410 ASSESSMENT OF ETHNIC VARIATION OF THIOPURINE S-METHYLTRANSFERASE ACTIVITY

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Background: Thiopurine S-methyl transferase (TPMT) partly predicts the activity and side effects of azathioprine. It is subject to trimodal distribution, with 90% of whites having normal, 10% intermediate, and 0.3% low or absent activity. Genotype population studies have demonstrated ethnic variation, with South West Asians, exhibiting significant variance from white people. Differences in phenotypic expression require further evaluation.

Methods: We have studied 500 consecutive patients presenting to an inner city teaching hospital phlebotomy service. TPMT activity was measured and compared with ethnicity.

Results: Samples were obtained from 232 white Europeans, 81 black Afro-Caribbeans and 176 Indo-Asians. Two white Europeans had absent TPMT activity, an incidence of 1:250. Activity ranged from 0–76 nmol 6-MTG/g Hb/hour with a median (interquartile range) of 33 nmol (29–38.75) 6-MTG/g Hb/hour. The median activity (and interquartile range) was lower in the black Afro-Caribbeans at 30 (26–36) nmol 6-MTG/g Hb/hour) than the white Europeans at 34 (29–39) nmol 6-MTG/g Hb/hour and Indo-Asians at 34 (30–39) nmol 6-MTG/g Hb/hour).

Conclusions: The similarities in activity between white Europeans and Indio-Asians is in contrast to the genotype analysis documented in the literature. Black Afro-Caribbeans appear to run a lower level of TPMT activity. Further studies with a larger population are required.

411 A SURVEY OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE ATTENDING GASTROENTEROLOGY OUTPATIENT DEPARTMENT

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Aims: An anonymous survey was performed at Southmead Hospital to ascertain patient preferences of the different types of outpatient services available.

Methods: Patients with inflammatory bowel disease (IBD attending the gastroenterology (GI) outpatient clinics between March 2001 and June 2001 were identified from case notes and then asked to complete the questionnaire which asked specifically about their preferred models of outpatient care. Patients were asked to rank from first to last choices for the following: daytime clinics, evening clinics, rapid access clinics, traditional clinics, telephone clinics, direct access to GI specialist services, GI Ansaphone helpline, outpatient self management plans, and which healthcare professional.

Results: Total number of questionnaires 118, no refusals, IBD patients 97%. There were 74% completed questionnaires. Age range 19–87, mean 45 (SD 15.5) years. The group comprised of patients with ulcerative colitis 60 (52%), Crohn's disease 45 (39.1%), IBD 45 (39.1%). 78 (67.8%) IBD patients said that they would be satisfied to see the nurse specialist review for routine clinic review. 92 (80%) preferred daytime clinics to evening clinics 19 (16.5%). Rapid access clinic appointment only with disease exacerbations and not maintaining routine specialist contact was the most popular choice (63.5%), followed by regular telephone specialist clinic review—that is, only attending clinic when necessary (23%) compared with attending regular routine specialist clinic (11.3%). If taking part in telephone clinics, 70%, preferred to discuss their health concerns with GI consultant first, followed by 16% with the specialist registrar, 9.6% with the nurse specialist, and 4.3% with any doctor. If they wanted rapid access to GI healthcare, 48 (41.7%) IBD patients would prefer GI Helpline to a person between the hours of 9am to 5pm, Monday to Friday, replies and advice within 24 hrs to 36 (31.3%) obtaining a clinic appointment within 1–2 weeks. If they were to telephone for advice about their condition, 84 (74%) would want to speak to their GI consultant, 13 (11.3%) with GI specialist registrar, and 10 (8.7%) GI nurse specialist, 1 (less than 1%) with GI secretary, and 6 (5.2%) for any doctor. With mild exacerbations of their disease, 82 (71%) wanted to be taught how to manage mild attacks with an agreed self management plan drawn up by their GI specialist

Conclusions: IBD patients are amenable to alternative models of healthcare and nurse specialist led services. They want better access to

GI specialist knowledge, preferentially from their GI consultant but happy to be treated by other healthcare personnel with in-depth knowledge of their condition. Previous patient surveys found that patients felt that specialist nurses have more time to discuss issues and they (the patients) do not want to bother the busy doctors with them. Are doctors now too busy to listen to their patients' concerns? Nurse specialists are good patient educators, and they reduce our workload by reinforcement and repetition of important clinical information. Self management plans most popular choice with 71% IBD patients selecting this over any of the other models of rapid access care.

412 LABORATORY MARKERS PREDICT BONE LOSS IN CROHN'S DISEASE: RELATION TO PBMC FUNCTION AND NUTRITIONAL STATUS

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Background and Methods: Crohn's disease (CD) is associated with an increased prevalence of osteoporosis. Identification of surrogate markers for bone loss in CD may have resource implications. We investigated the relation of simple markers of inflammation with markers of bone turnover, nutritional status, and cytokine production by peripheral blood mononuclear cells (PBMC), in a case control study in CD. Urinary deoxypyridinoline (DPD/Cre; bone resorption) and serum osteocalcin (bone formation) concentrations were compared in male and pre-menopausal females with ''active'' CD (CRP>10 and/or ESR>20) (n=22) and unmatched controls with ''quiescent'' CD (CRP<10 and ESR<20) (n=21). A secondary analysis was performed using the CDAI. Production of tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and prostaglandin E_2 (PGE_2) by PBMC were measured by ELISA following stimulation with LPS and Con A.

Results: Active CD was associated with higher DPD/Cre ($P=0.02$) and a higher DPD/Cre:osteocalcin ratio ($p=0.01$) compared with quiescent CD, but similar osteocalcin ($p=0.24$). Differences between active and quiescent CD were not explained by vitamin D status, dietary intake or nutritional status, however production of IFN-γ by Con A stimulated PBMC was lower in active CD ($p=0.02$) and correlated negatively with the DPD/Cre:osteocalcin ratio ($r=-0.40$, $p=0.02$). There was no relation between bone turnover and CDAI.

Conclusion: Raised simple laboratory markers of inflammation, CRP and ESR, are associated with higher rates of bone loss in CD. Inflammatory activity in CD may influence bone turnover by altered production of IFN-γ by PBMC, but the influence of nutritional status is uncertain. CRP and ESR, but not CDAI, may be valuable tools for stratifying CD patients with respect to the risk of osteoporotic fractures, and should be evaluated in a multicentre, prospective study.

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413 AUDIT ON NEW CONSENT FORM—MORE CONFUSION THAN HELP

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Introduction: Over the last 35 years informed consent for medical procedures has been transformed from an ethical concept to a legal requirement. The information in an ideal consent form should be clear, informal, and understandable to the lay person, avoiding the use of jargon. As a part of good practice, the Department of Health introduced new consent forms for examination or treatment from April 2002. To our knowledge there are no reports of feasibility of this new consent form in present day practice.

Aims and Objectives: To analyse the completeness of recorded information on the new consent form for patients undergoing endoscopic procedures.

Methods: The consent forms of 160 patients who had undergone GI endoscopy procedures in last 3 months were analysed retrospectively.

Results: In 160 patients there were 53% males and 47% females; the commonest procedure was OGD followed by colonoscopy. Most of the time the consent and procedure were done by consultants (72% & 78%), followed by registrars (25% & 22%). Patients' details were present in 96% of forms, use of black biro in 98%, health professional name in 86%, and title and proposed procedure in 99%.

In most of the forms health professional had explained the benefits (81%) and risks involved in the procedures (91%); however only 14% had explained about requirement of extra procedure and 11% had mentioned about the leaflets provided. The sedation requirement was mentioned in 66% but not in 28% who in fact had sedation for the procedures. In 98% of the forms the signature was complete with name printed and dated. Surprisingly in the majority of patients (96%) there was no mention about acceptance of consent copy and contact details of the patients (71%). This is important if one wishes to discuss therapy later. Only 71% of forms had complete patient's signature; the majority of incomplete signatures were either with out printed name or dates.

Conclusion: In the statement of health professional, the majority of forms mentioned intended benefits and risks, had complete signature but only a minority mentioned possible extra procedures or whether a leaflet was provided. In nearly one third of forms there was no mention of sedation. In almost all patients there was no mention about acceptance of consent copy and majority missed contact details with incomplete patient signature. We believe that the new consent form seeks too much information for us to complete it properly, within the current service framework. We now plan to compare this group with the previous procedure specific consent form and establish whether there is a significant difference in correct form completion. We shall also prospectively audit the time taken to acquire informed consent, develop a tool to measure the quality of consent, and explore new methods of providing informed consent.

414 WHAT DOES A GASTROENTEROLOGIST COST?

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Background: Recent expansion of the consultant grade is usually on an ''activity neutral'' basis with funding groups providing consultant and secretaries salaries only. However, new appointments can result in significant additional expenditure but assessment of this is hampered by lack of reliable information in the National Health Service. For example, the national schedule of reference costs shows the reported cost of ERCP in different trusts to vary from £37 to £808.

Methods: To try and assess all the consequential costs of a consultant appointment, we have prospectively studied the work of one gastroenterologist in a busy non-teaching hospital for 6 months. All new patients were followed up and any investigations recorded. With the help of our hospital finance department we have attempted to find the cost of each test in our hospital. We have calculated the cost of running the outpatient clinics and endoscopy unit including support staff, capital charges, and management costs. The study did not include the general medical emergency service or gastroenterology inpatients.

Results: 563 new outpatients were seen and all but 17 had at least one investigation. 67 different tests were ordered ranging from a full blood count (£3) to MRI scan (£489). In a full year one consultant's outpatient clinics will generate requests for 500 gastroscopies (£164 000), 282 ultrasounds (£8584), 190 barium enemas (£13 881), 116 flexible sigmoidoscopies (£38 048), and 104 colonoscopies (£38 480). The cost of providing 3 outpatient clinics a week for 1 year excluding consequential endoscopies was estimated to be £280 287. The endoscopy unit costs £911 011 each year. Two gastroenterologists and their junior staff provide 14 sessions (cost per session per annum: £65 072). Excluding fixed overheads it will still cost £204 460 to provide 3 new outpatient clinics a year and each extra endoscopy session will cost £52 505.

Conclusion: We estimate the true cost of a new gastroenterologist (including salary, secretarial support, junior staff, and new clinics) to be over £450 000.

415 ARE WE DUPLICATING THE WORK DONE ON THE WARD? A COMPARISION OF GENERIC HISTORY TAKING OF HOUSE OFFICERS AND THE NURSING STAFF

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Introduction: The implementation of the European Working Time Directive recommendations in August 2004 will dramatically reduce the junior doctors' working hours and new ways of working will need to be found. It is known that nurses and doctors both record details of past medical history, social and family history, current medication and allergies, and vital signs (''generic history'') sometimes within minutes of

each other. The aim of this study was to establish whether this information could be recorded by nurses only with a view to reducing the amount of unnecessary duplicate data entry.

Methods: A prospective study of 100 case notes from elective and emergency admissions was undertaken. Completeness of various parts of the history and the recording of the vital signs was compared between nurses and house officers.

Results: The past medical history was complete in only 30% of the house officers' notes and 42% of nursing records. The social history was complete in all the nursing records but only 35% of the doctors' notes. Nurses recorded a complete personal history more than the doctors (62% *v* 13% respectively). The drug history was poorly recorded in house officers' notes being complete in 22% whereas this was complete in 73% of nursing records. The record of the history of allergies was poor in both the groups at just over 10%. Finally 87% nurses managed to record vital signs but these were missing from nearly half of the house officers' notes.

Conclusion: This study has shown that the nursing staff record the details of the generic medical history more completely. The age old tradition of a nurse taking the history followed shortly by the house officer repeating some of the same questions should be abandoned. This is unnecessary duplication of the work that should be done either of them. We therefore suggest that the generic medical history should be recorded once by the admitting nurse. This information should be available in the medical notes together with the baseline vital signs. This will prevent unnecessary duplication of effort by the house officers and allow them to concentrate on areas where their expertise is needed.

416 THE NURSE LED DYSPEPSIA CLINIC: A COMPARISON WITH THE MEDICAL MODEL

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Background: Over 35% of primary care referrals to our department are for patients with dyspepsia. In an attempt to reduce outpatient waiting lists, we set up a nurse led dyspepsia clinic. A consultant identified suitable primary care referrals and patients seen by a specialist nurse (SpN) were interviewed in a clinic run in parallel with a specialist registrar (SpR) and consultant. Patients were interviewed by the SpN according to a proforma set up for the management of patients with dyspepsia. The aim of this study was to compare the performance of this service with the standard medical outpatient model.

Methods: The notes of all new patients seen in a single outpatient clinic between January and July 2002 were reviewed. Patient demographics, advocacy requirements, the presence of alarm symptoms, *H pylori* status, investigations requested, treatment prescribed, final diagnosis on discharge, and missed diagnoses for the SpN, SpR, and consultant were determined. Patient and primary care physician dissatisfaction with the nurse led clinic were recorded.

Results: The SpN, SpR, and consultant saw a total of 91, 33, and 124 patients, respectively. Patient demographics were similar in all three groups. The advocacy requirements, presence of alarm symptoms, and *H pylori* status were also similar. The SpN and consultant requested significantly fewer investigations compared with the SpR. Treatments prescribed were similar in all three groups, as were final diagnoses on discharge. Significant incidental findings were also similar in all three groups. The SpR missed no diagnoses, the SpN missed one (1.1%) diagnosis (biliary colic), and there were three (2.4%) missed diagnoses (biliary colic, duodenal ulcer, diabetes mellitus) by the consultant. Over the period of the study, there was a single dissatisfied patient, and no dissatisfied primary care physicians. There were no re-referrals to a consultant of patients seen by the SpN for the period of the study.

Conclusions: The nurse led dyspepsia clinic performs well and may be a suitable alternative compared with the classic medical model.

417 AN ASSESSMENT OF A NURSE LED BARRETT'S OESOPHAGUS FOLLOW UP CLINIC

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Introduction: Barrett's oesophagus is a common problem, often diagnosed at open access endoscopy. Surveillance endoscopy to identify dysplasia is usually undertaken in all patients. Guidelines are available for the management of Barrett's oesophagus which cover medical, surgical, and ablative therapies together with guidance on the frequency of surveillance endoscopy. It is likely that many centres will have an unstructured approach to surveillance and assessment of these patients.

Methods: Patients with a new diagnosis and those undergoing routine surveillance for Barrett's oesophagus were referred to a nurse led clinic. At the clinic visit, patients were assessed per protocol for; general health, compliance with anti-reflux medication, and the validity of the diagnosis of Barrett's oesophagus. Patients were given an explanation and written information about Barrett's oesophagus, lifestyle advice, and information about research protocols, surgical and ablation treatments. The patients were assessed regarding potential surgical intervention, counselled regarding further investigation and surveillance, particular emphasis on the future development of alarm symptoms was made. An evidence based management plan was the agreed with the patient.

Results: Of the first 45 patients: (32 males aged 28–85 years median 58.5 years, 13 females aged 46–83 years median 62 years), important observations have been made; 2 surveillance patients had no evidence of Barrett's oesophagus. Current comorbidity included: 10 ischaemic heart disease, 6 respiratory disease, 9 other precluding surgery. Five were non-compliant with medication, 8 had reflux symptoms, 6 would decline surgery even if offered. Five patients were referred for pH/manometry anticipating anti-reflux surgery. All patients agreed to admission onto the UK Barrett's registry.

Conclusions: This clinic can be nurse led and structured to identify significant treatment and management issues. Patients are often recruited from open access endoscopy and this clinic provides an opportunity for patient education and involvement. A structured approach to the management of this chronic condition should optimise and individualise treatment and prove cost effective to the health care economy.

418 INFLUENCE OF PRIMARY CARE CHARACTERISTICS ON REFERRAL AND OUTCOME IN A RAPID ACCESS UPPER GI CANCER SERVICE

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Background: Dyspepsia is responsible for 5% of consultations in primary care in the UK but each general practitioner (GP) will see just one new case of upper GI cancer per year. National guidelines specify predetermined alarm features meriting urgent referral under the ''two week rule''. Guideline compliance and referral practice is known to vary widely in primary care. We aimed to investigate the contribution of practice characteristics to variation in referral rate and yield of pathology in a well publicised rapid access upper GI cancer service (RAUGICS).

Methods: Details of all referrals to the fast track service were recorded prospectively, including demographics, referral indications (from standard referral proforma), and outcome. Practice information regarding partner number, list size, training status, level of deprivation in the practice population, and practice referral rate to hospital gastroenterology outpatient clinics was collected. Data were analysed over a 27 month period. Outlier practices with less than 3 outpatient referrals or 1 RAUGICS referral were excluded. Spearman correlation coefficent analysis (SPSS 10.1) was used to determine influence of practice characteristics upon referral rate and diagnosis.

Results: 3175 referrals from 78 practices were included (yield: 2.5% cancers; 13.2% ''pathology'' (CA, PUD, strictures, severe oesophagitis)). Referral volume varied substantially (1–200) but this variation was largely independent of practice characteristics (see table). Yield of significant pathology or cancer at endoscopy did not have any significant correlation with practice referral rate.

Conclusions: The large variation in referrals from primary care is not adequately accounted for by simple practice characteristics. There was no effect of referral volume per practice upon endoscopy findings suggesting high referral practices may still be referring appropriately. Relatively poor cancer yield of RAUGICS is unlikely to be simply due to

Abstract 418

	Referral rate*	Cancer per referral	Serious pathology per referral	Proportion referrals <55 yrs
Referral rate*		0.11	0.09	−0.092
No of partners	0.37	0.181	−0.09	−0.193
Training practice	0.207	−0.074	−0.145	−0.037
% Deprived pts*	−0.096	0.22	0.33	0.214
OPD referrals*	0.26	−0.012	−0.051	−0.054

*Standarised rate per 1000 practice population.
Significant if Spearman's Rho correlation coefficient >0.5.

variation in patterns of referral from primary care but may relate to poor specificity of referral features.

419 THE DYSPHAGIA HOTLINE

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Background: Dysphagia is an alarm symptom that should prompt urgent referral to exclude carcinoma of the oesophagus, and is a symptom which justifiably prompts GPs to refer patients under the 2 week cancer rule.

Aims: To determine the incidence of true dysphagia (the sensation of ''sticking'' when solids or liquids are swallowed) in patients referred with dysphagia under the 2 week rule and to assess the improvement in patient service with the implementation of a dysphagia hotline.

Methods: A ''dysphagia hotline'' was piloted for 6 months. 92 patients were referred with dysphagia under the existing 2 week cancer guidelines. A telephone consultation was conducted with the patient by a consultant gastroenterologist. All patients were then seen in a dysphagia clinic and underwent a barium swallow *x* ray. Patients with possible malignancies on barium swallow then received 10 mg metoclopramide together with 100 ml diet cola and two hours later attended the endoscopy unit for a diagnostic upper GI endoscopy.

Results: 30/92 (32.6%) had true dysphagia. 7/92 patients had oesophageal cancer, all of whom had true dysphagia. Other diagnoses included GORD (n = 37), peptic stricture (n = 8), globus (n = 9), dysmotility (n = 7), pharyngeal pouch (n = 3), Schatzki ring (n = 4), Ca stomach (n = 1), cricopharyngeal spasm (n = 2), indeterminate (n = 14). Logistic regression analysis showed that the most reliable predictor of the presence of malignancy is the presence of progressive symptoms in a patient with true dysphagia (relative risk 18.6: 95% confidence interval 2.42 to 143.5). Following the introduction of the dysphagia hotline the mean time from referral to diagnosis significantly improved from 29.8 to 13.6 days (95% confidence interval −22.6 to −9.64).

Conclusions: Over 60% of patients referred with dysphagia under the 2 week rule do not have dysphagia. True progressive dysphagia carries a relative risk of 18.6 for having oesophageal cancer. The dysphagia hotline significantly shortens time from referral to diagnosis, but is unlikely to affect outcome.

420 A POOLED AND PRIORITISED DYSPHAGIA REFERRAL SERVICE: AUDIT OF THE FIRST NINE MONTHS

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Introduction: Dysphagia is an ''alarm'' symptom: such patients require prompt assessment, investigation and treatment. However, referral patterns and numbers to individual clinicians vary unpredictably, making it difficult to respond consistently to urgent need.

Methods: To reduce variability, we produced a standard ''Dysphagia Referral Form''. These ask for standard patient information plus 6 questions considered by us to form a ''minimum data set'' to determine action. The forms were introduced in January 2003 and sent, with covering explanation, to all GPs who care for our 300 000 catchment area. A referral audit for key GI symptoms, performed prior to the study, predicted 16–20 dysphagia referrals per month. Referrals are sent in to a centralised fax then distributed sequentially, allowing for periods of leave, to the 4 consultants within the unit. Each consultant determines onward management.

Results: In the first 9 months, 74 patients (34 female) were referred, using the form, at a rate of 6/month in the first 6 months and 12/month for the last 3. Average age: 66 years. On average, it took 19 days (21 for first 6 months ; 16 for last 3 months) for the first contact with our unit. This was a gastroscopy in 48, clinic in 24 and emergency admission in 2. On average, it took 28 days (35 in first 6 months; 20 in last 3 months) for patients to have their first test. The first test chosen was a gastroscopy in 68 patients, barium swallow in 3, oesophageal pH/manometry study in 1 (with 2 patients failing to attend clinic and therefore not being offered any test).

There were endoscopic abnormalities, mostly oesophagitis, in 44 (61%) but including 7 cancers (10%). Of the remaining patients a clinical diagnosis, mostly GORD, was made in 17 patients (with 11 awaiting further tests—for example, pH/manometry—prior to formal diagnosis).

Conclusions: Referrals increased as GPs became familiar with the system; a reduction in time to first contact and test as consultants improved efficiency; service now provides a diagnostic test within 3 weeks of referral. These results encourage us to offer a more coordinated pathway and improve our service for dysphagia patients.

421 IMPORTANT IMPLICATIONS OF TWO WEEK WAIT ARE NOT BEING REPORTED

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Introduction: The aim of the ''two week wait'' (TWW) is to improve the outcome for patients suspected of having cancer. There is some evidence that gastroenterologists perceive that the TWW has been a negative service development. We aimed to determine if selected ''critical information'' is included in reports on TWW to indicate if it is achieving its aim.

Methods: We quantitatively and qualitatively analysed all papers relating to the TWW presented to this Society from 2001 to 2003. Abstracts were searched for a predetermined minimum data set of information (see table). Papers were classified as ''positive'', ''negative'' if authors concluded that TTW brought local benefit or harm. Conflicting conclusions were classified as ''neutral''.

Results: Since 2001, 21 of 1310 papers (1.6%) presented to the Society have reported on the TWW, 5 in 2001, 8 (2 plenary) in 2002, and 8 (2 plenary) in 2003. Prospective data have been reported on 5820 patients, representing 140 months of audited activity.

None of the abstracts reported on all the listed criteria, the majority mentioned only two. Most reported on the process of TWW implementation rather than its impact. One concluded that the TWW was an exclusively positive development, nine that it was detrimental, and eleven papers that TWW brought benefit and harm in tandem. A Medline search confirmed that the results have not been published in peer review journals.

Conclusion: Gastroenterologists who report their experience with the TWW either perceive it as a negative development, or as having a mixed impact on service provision. Major impacts that may reasonably be of interest in the assessment of the efficacy of the TWW are not reported to the BSG or a wider audience.

Abstract 421

Aspects of the 2 week wait	No (%) of papers reporting
Cancer (Ca) yield for TWW	14 (66.7%)
Yield as proportion of all Ca	8 (38.1%)
Time to treatment for TWW	2 (9.5%)
Time to treatment for other patients	1 (4.7%)
Delay to other patients	6 (28.6%)

422 MANAGEMENT OF UPPER GASTROINTESTINAL CANCERS: HOW ARE WE DOING?

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Background: The theme of the ''NHS Cancer Plan'' is earlier diagnosis and treatment of cancers. This is more so important in upper gastrointestinal (GI) cancers where the prognosis remains worse despite advances in treatment and hence a ''very early diagnosis'' is the key.

Aims and Methods: To study all patients diagnosed to have upper GI cancer in our hospital over a 12 month period. Patients were identified from pathology and MDT records and data were obtained from the hospital notes.

Results: 65 patients (28 females) were identified. The mean age was 71 years (range 43–86) for males and 75 years (range 54–96) for females. 58 patients were directly referred from GPs whereas 7 were inhospital referrals. There were 37 oesophageal cancers, 21 gastric cancers, and 7 pancreatic cancers. 13 (20%) cancers (8 oesophagus, 5 stomach) were identified on open access endoscopies, 10 (15%) (5 oesophagus, 5 stomach) in standard outpatient referrals, 25 (39%) (19 oesophagus, 2 stomach, 4 pancreatic) on 2 week wait referrals and 17 (26%) (5 oesophagus, 9 stomach, 3 pancreas) at routine endoscopies or investigations on inpatients. 36 (55%) patients were seen within 2 weeks of referral and 45 (69%) within 4 weeks. 47 (72%) patients had investigations within 2 weeks of consultation. 56 (86%) had been diagnosed within 4 weeks and 45 (69%) patients had a diagnosis within 2 weeks of referral. 29 (15 oesophagus, 13 stomach, 1 pancreas) underwent resection of tumours while 36 (22 oesophagus, 8 stomach, 6 pancreas) needed palliation.

Conclusion: Earlier diagnosis and treatment of upper GI cancers remains a challenge. Despite majority (86%) of patients having had a

diagnosis within 4 weeks only 45% were resected. This might reflect delayed referral from primary care or patient unawareness to seek help earlier, the latter being most likely.

Abstract 422 Median duration between referral to outpatients, consultation, and diagnosis

	Referral–OPD	Referral–investigation	Referral–diagnosis
All cancers	10 (1–70)	8 (1–70)	9 (1–75)
Oesophagus (37)	9.5 (1–60)	8 (1–60)	9.5 (4–60)
Stomach (21)	22 (4–70)	11.5 (1–70)	12.5 (2–75)
Pancreas (7)	9 (5–11)	5 (2–26)	5 (2–40)

423 A DIETITIAN LED COELIAC FOLLOW UP CLINIC IS PREFERRED BY PATIENTS AND RELEASES OUTPATIENT CLINIC SLOTS

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Background: It is good clinical practice, and a recommendation of the BSG, that patients with coeliac disease are regularly followed up. Assessment at review should include nutritional status, dietary compliance, routine bloods, and to look out for any complications. However, demand on gastroenterology clinics continues to increase, making this goal difficult to achieve. We felt that long term follow up of these patients could be shared with a GI dietitian with a specific interest in coeliac disease.

Methods: We therefore set up a protocol driven dietitian led coeliac clinic, alternating 12 month follow up appointments between the medical team and our GI dietitian. At these visits patients discuss their clinical status and diet. Routine bloods including EMA are checked. Any specific concerns can be discussed with an available consultant.

Discussion: The clinic began January 2002, with a steady increase in the numbers seen. To date 74 patients have been seen in this clinic, releasing corresponding gastroenterology clinic slots. The numbers have gradually increased over this period of time.

We carried out a postal questionnaire to gauge patients' satisfaction with this new system. 53 questionnaires were sent out and 35 replies were received. 90% of patients preferred the new system. Specific reasons included the opportunity to discuss diet in detail, a longer appointment and reduced waiting times, particularly on the day of appointment. Only 6% stated that they would prefer to see a doctor each visit.

Conclusion: In summary our dietitian led coeliac clinic appears to work well, releases slots in gastroenterology clinics and is preferred by patients.

424 THE VALUE OF THE SINGLE CONSULTATION IN A CHRONIC FUNCTIONAL ABDOMINAL PAIN CLINIC

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Background: Chronic functional abdominal pain is a common and difficult to treat complaint in gastroenterology clinics. The value of a single definitive consultation in patients with functional somatic syndromes has been previously shown. The content of this consultation is manifold, including explanation of pathophysiology, addressing of psychological issues and teaching of relaxation and simple distraction techniques. We describe the value of a single such consultation in patients seen in a specialist chronic abdominal pain clinic.

Methods: 286 (201 women; mean age 33, range 18–79) consecutive patients with chronic functional abdominal pain were seen in a specialist clinic. Prior to initial assessment and at yearly intervals, patients completed the following questionnaires: Brief Pain Inventory (BPI), SF-36 quality of life tool and Hospital Anxiety and Depression scale (HAD). All patients were seen for an initial consultation, of about one hour. 94 patients (33%) were offered a single appointment (SA) only, based on their ability to understand pathophysiology, follow a weaning regime and pursue psychological support. Two year follow up data are available in 38/43 patients who have reached that point and in 55/64 at 1 year. (The other 192 patients (67%) received pharmacological or physical interventions, and were offered conventional follow up.)

Results: In the SA group, pain intensity fell significantly compared to baseline (1 year 7.4 (SD 1) to 4.1 (SD 0.8), 2 years 7.8 (SD 1.2) to 3.6 (SD 1), $p<0.01$). BPI scores of walking, ability to leave home and to sleep, and SF-36 scores of body pain and social function were all improved at 1 and 2 years questionnaires compared with baseline ($p<0.03$ for all). HAD scores of anxiety were reduced (16 (SD 4) to 9 (SD 3), 15.1 (SD 3) to 8 (SD 3) baseline *v* 1 and 2 years respectively, $p<0.01$) whereas depression scores were not altered. 64% of patients were consuming opiate drugs at baseline, which fell to 31% at 1 year and 29% at 2 years after a single assessment visit. Annual GP consultation rates fell from median 10 to 7 (baseline *v* 2 years).

Discussion: A single definitive assessment is an effective and efficient intervention for some patients with chronic functional abdominal pain.

425 DOES TEACHING INFLUENCE COLONOSCOPY COMPLETION RATES?

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Introduction: Audited colonoscopy completion rates are less than 90%. We explored whether trainees learning colonoscopy influenced the completion rate or the time taken for the procedure.

Method: We prospectively audited the caecal and terminal ileal intubation rates and the procedural time for 227 consecutive procedures over 2 months. 68 procedures were performed by a trainee, 9 of these by an experienced trainee without direct consultant supervision. Patients were not selected specifically for training lists but the number of procedures on such lists was reduced.

Results: Consultants performed 8–30 procedures alone and 3–18 with trainees.

There was a trend for those performing most procedures to have higher caecal intubation rates but no difference in duration of procedure. Duration of procedure was generally shorter for procedures performed by surgeons, especially where trainees were involved.

Conclusions: Teaching a trainee colonoscopy does not reduce completeness of the examination, indeed there was a trend for it to increase. It markedly increases the average duration of the procedure which has obvious resource implications.

Abstract 425

	Caecal intubation	TI intubation	Average procedure time (minutes)
Consultants alone	78%	29%	29.8
Medical consultants	89–97%	44–69%	27–28
Surgical consultants	14–85%	0–14%	18–39
Clinical assistant	87%	23%	30
All trainees	84%	33%	41.7
Medical trainee (supervised)	77–92%	46–60%	47–49
Medical trainee (unsupervised)	78%	11%	40
Surgical trainee (supervised)	78–100%	0%	28–31

426 A NURSE LED OPEN ACCESS SERVICE FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE IMPROVES PATIENT CARE IN A DISTRICT GENERAL HOSPITAL

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Backgound: After the appointment of an inflammatory bowel disease (IBD) Nurse Specialist in 2002, process mapping and a patient satisfaction survey revealed delayed management in both primary and secondary care, resulting in prolonged periods of ill health and patients receiving subtherapeutic doses of medication, or attempting to self medicate.

Methods: A telephone helpline was established to enable direct referral from GPs and patients, and to provide an information resource. Dedicated nurse specialist led clinic slots were established to facilitate early review of patients with disease exacerbations and the activity was audited over the first six months.

Results: A 6 month audit revealed that a total of 222 patients contacted the open access service. 71 patients contacted with a new exacerbation or refractory disease. Of these 66 were referred to clinic and were seen within five working days (the remainder had an appointment within 10 days and were able to follow verbal telephone orders), compared to a mean of 8 weeks beforehand. 151 contacted the service for general information regarding diagnosis and management. All patients used the service appropriately. Patient evaluation groups reinforced increased satisfaction with the service, improvement in patient education, feelings of wellbeing and quality of life. Primarily patients believed this was achieved through earlier therapeutic management limiting the impact of their condition upon physical wellbeing, work and home life with an overall improved quality of life.

Conclusion: The development of a nurse specialist led open access service for patients with IBD has facilitated a major improvement in the quality of patient care.

427 PATIENTS' VIEWS OF THE INFLAMMATORY BOWEL DISEASE SERVICE

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Aims: Different means for outpatient services of inflammatory bowel disease (IBD) follow up have been proposed.[1] We sought to establish patients' views on the IBD service in the North Trent region.

Methods: The opinions of National Association for Colitis and Crohn's disease (NACC) members in the North Trent region were sought by means of anonymous postal questionnaires. The importance of different aspects of current and future practice were assessed on a visual analogue scale from 0 (being the worst) to 10 (being the best).

Results: Four hundred and thirteen NACC members responded, of which 237 patients had Crohn's disease (CD) and 176 ulcerative colitis (UC). The median age was 50 years with a 63.4% female preponderance. 166 (40.2%) patients preferred to see a doctor; the majority (59.8%) were equally happy to see a nurse specialist. Mean scores in order of importance were: advice and treatment that improves symptoms (9.48), clear explanations (9.45), a clinician who listens and understands (9.35), the ability to get an appointment quickly (8.97), adequate consultation times (8.07), and continuity of personnel (8.02). Less important concerns included appointment times (6.12), being seen regularly even when well (6.80), the facility to reschedule an appointment (6.82), and dietary advice (7.32) ($p<0.01$, ANOVA). Patients expressed interest in the following: self management protocols (86.6%), telephone consultations (78.2%), evening/weekend clinics (70.0%), group sessions (52.1%), and email consultations (38.5%).

Conclusions: Patients are clearly interested in new methods of interaction with clinicians, but they want health professionals to be accessible, communicate with them, and most importantly make them better. Patient centred audit and the introduction of new approaches in the IBD service may allow us to work towards these goals.

1. **Robinson A**, *et al. Lancet* 2001;**358**:976–81.

428 DIRECT ACCESS COLONOSCOPY VERSUS OUTPATIENT APPOINTMENTS FOR TWO WEEK RULE REFERRALS: PATIENT SATISFACTION SURVEY

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Introduction: Flexibility of appointments for investigations and patient choice has been advocated as the NHS moves towards patient oriented care.

Methods: A postal satisfaction survey was conducted on 170 patients who had been referred via the two week rule pathway over a three month period from June 2003. Direct access colonoscopy or outpatient consultation was arranged at the discretion of the referring general practitioner. Information was given and fitness for colonoscopy confirmed by the nurse endoscopist by telephone.

Results: 127 (75%) questionnaires were returned. 13 were incomplete and excluded. The M:F ratio was 37:77. The average age was 59 years. Out of the 114 patients 60 patients were referred for direct access colonoscopy and 54 patients were seen in outpatient clinics. 108 (95%) patients were offered a choice of appointment or choice of hospital. Of 60 patients who underwent direct access colonoscopy only 4 (6.6%) expressed a desire to be seen at outpatients initially. 112 (98%) patients were satisfied with the service provided.

Conclusions: Offering patients a choice for outpatient appointments and investigations is feasible. Patients can be directly admitted in for investigations bypassing the outpatient clinic without affecting patient satisfaction. This may be the way forward as the NHS starts to offer more choice for patients as evidenced by the recently introduced patient choice scheme.

429 TWO WEEK RULE CANCER REFERRAL: DIRECT ENDOSCOPY VERSUS OUTPATIENT ASSESSMENT

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Background: In January 2001 the two week rule for colorectal cancer referrals was implemented, giving UK general practitioners the onus to determine urgency for assessment. In our trust, GPs were given the option of outpatient clinic review or direct referral for colonoscopic assessment, both within the two week wait.

Aim: To prospectively audit the referral pattern within the two week rule, comparing the efficacy of direct access colonoscopy with urgent outpatient assessment.

Method: Over a 4 month period (March to June 2003 inclusive) data were collected on all patients referred under the two week rule in our trust. Date and mode of referral, date of assessment, endoscopy, follow up, and histological diagnosis were all recorded. We then compared direct access endoscopy with outpatient review with regards to speed of investigation, tissue diagnosis, and treatment, for those patients found to have colorectal malignancy.

Results: 215 patients were referred of whom 9 were excluded. Of the 206 remaining referrals, 70 = direct colonoscopy and 136 = outpatient clinic.

From referral to first seen the median times were comparable in both groups (colonoscopy = 9 days and outpatient = 8 days). Of the patients referred for outpatient review, colonoscopy was indicated in 103 patients, median time from referral to colonoscopy was 44 days.

In patients with a diagnosis of colorectal cancer median time from referral to histological diagnosis was 14.5 days in direct colonoscopy versus 25.5 days outpatient clinic ($p<0.01$) and median time from referral to first treatment was 48 days versus 85 days ($p<0.01$).

Conclusion: Referring patients directly for colonoscopy bypassing the traditional outpatient assessment leads to significantly reduced waiting times for histological diagnosis and commencement of treatment in patients with colorectal cancer referred under the two week rule.

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430 MEASUREMENT OF LOWER OESOPHAGEAL SPHINCTER PRESSURE: COMPARISON OF THREE TECHNIQUES

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Background: Three techniques of lower oesophageal sphincter pressure (LOSP) measurement exist: rapid pull through (RPT), station pull through (SPT), and Dent sleeve (DS). Only RPT and SPT have been compared suggesting SPT to be more reproducible, but all 3 have not been compared previously.

Methods: 44 patients (24 men, mean age 44 yrs (22–68)) undergoing oesophageal function studies. Purpose built catheter (standard microcapillary channel array and Dent sleeve). Measurements carried out twice: at start and end of manometry study. For RPT and SPT, 4 channels at 90° radial intervals at same level on catheter were used. Baseline was

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Method	Mean pressures (SE), start (mm Hg)*	Mean pressures (SE), end (mm Hg)	Correlation coefficient (*r*)
SPT	23.3 (1.73)[1,2]	28.2 (1.88)	0.53†
RPT	13.1 (0.77)	12.8 (0.7)	0.58†
DS	10.7 (1.2)	11.9 (1.3)	0.66†

*ANOVA $f = 27.4$; $p<0.0001$; [1]SPT *v* RPT (Scheffe $F = 15.98$, $p<0.05$) [2]SPT *v* DS (Scheffe $F = 27$, $p<0.05$) Paired measurements (start *v* end) by each test were significantly correlated (†$p<0.001$) but *r* values were only 0.53–0.66.

intragastric pressure. No swallows allowed during LOSP measurements. **RPT:** three pull throughs, held expiration. Peak to baseline measurements for all channels averaged. **SPT:** catheter withdrawn during quiet respiration through LOS (1 cm per minute). Highest pressure in each channel selected; expiratory phase pressure measured and averaged. **DS:** gastric baseline to expiratory phase pressure averaged over a period of five minutes.

Results: see table.

Conclusions: No method is particularly reproducible but DS and RPT show least variability. SPT gives consistently higher measurements than both DS and RPT while measurements by DS and RPT were not significantly different.

431 ESTIMATED OESOPHAGEAL CLEARANCE, LUMEN DIAMETER, AND GORD

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Background and Aims: Oesophageal clearance is an important mechanism of defence against gastro-oesophageal reflux disease (GORD). The study aims were to investigate the role of oesophageal clearance in patients with GORD and consider the effects of oesophageal lumen diameter and hiatus hernias (HH).

Methods: Percentage clearance of barium was estimated from a frame by frame review of five barium swallows for 31 patients with a clinical diagnosis of GORD. The maximum oesophageal lumen diameters were measured using manometry transducers as reference points. Ambulatory 24 hour pH monitoring was carried out following the radiology study. The presence of an HH was noted from patient records.

Results: Patients with pathological reflux on pH testing had a reduction in estimated oesophageal clearance ($p<0.01$) reducing from 88% to 80%. No difference was found in estimated clearance between patients with and without oesophagitis. There was a slight difference in distal maximum lumen diameter in patients with (1.51 cm) and without pathological reflux (1.68 cm), $p=0.093$. In the subpopulation of patients with pathological reflux, estimated clearance was greater in patients with a HH than in patients without ($p=0.01$). In patients with a HH, the distal lumen diameter was larger (1.65 cm) compared to patients without a HH (1.49 cm), $p=0.077$.

Conclusion: The reduction in estimated clearance was confirmed in patients with pathological reflux. Interestingly, the distal lumen diameter was smaller in patients with pathological reflux. For a given volume of reflux a narrower lumen will cause the refluxate to rise further up the oesophagus and therefore may account for this result. Alternatively this may be accounted for by pathological changes in the physiology of the lumen walls such as inflammation.

The analysis used a pathological reflux threshold of 6 and 4 for percentage total exposure time.

432 AUDIT OF A STATEWIDE OESOPHAGEAL MANOMETRY AND PH SERVICES

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Background: The oeosphageal laboratory in Royal Perth Hospital was established in 1991 to provide oesophageal manometry and pH monitoring service for the state of Western Australia.

Aims: To review referral and diagnosis patterns of oesophageal manometry and pH studies over a 12 year period.

Methods: Referral indications and diagnoses of all 2618 oesophageal manometry and 1556 pH studies performed between 1991 and 2002 were obtained from the oesophageal laboratory database. Indications and diagnoses in the first and second 6 year periods were compared.

Results: Indications for manometry were gastro-oesophageal reflux disease (GORD) 32.1%, dysphagia 28.2%, preoperative assessment 16.2%, chest pain 13.6%, and ''other'' 9.9%. Manometry performed for preoperative assessment increased from 8.7% in the first 6 year period to 22% in the second 6 year period ($p<0.0001$). Manometric diagnoses were non-specific oesophageal motility disorder (NSMD) 42.4%, normal 28.8%, achalasia 9.5%, diffuse oesophageal spasm 3.7%, nutcracker oesophagus 2.1%, and ''other'' 13.6%. The commonest diagnosis in patients referred with GORD, dysphagia and preoperative assessment was NSMD. Manometry studies were normal in 43.3% of patients referred with chest pain. Indications for pH study were classical reflux symptoms 38%, atypical reflux symptoms 26%, preoperative assessment 25.2%, dysphagia 6.5%, and ''other'' 4.4%. pH study performed for investigation of classical reflux symptoms increased from 33% in the first 6 year period to 41.6% in the second 6 year period ($p<0.0001$). pH studies were normal in 42.2%, normal with positive symptom index (SI >50%) in 4.8%, abnormal in 25.6% and abnormal with positive SI in 27.5%. For preoperative assessment patients, pH study was normal in 23.1%, normal with positive SI in 4.7%, abnormal in 26%, and abnormal with positive SI in 46.2%.

Conclusions: Oesophageal manometry is increasingly being done as part of the work up for fundoplication. pH studies in patients considered for antireflux surgery are often normal.

433 IS PHARYNGEAL PH THRESHOLD IMPORTANT FOR DETECTING DENTAL EROSION?

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Introduction: Patients with hoarseness, globus, dental erosion, asthma, or chronic cough have been suspected to have distal and proximal gastro-oesophageal reflux (GOR). This study aimed to investigate the association of pharyngeal pH with dental erosion in these patients.

Method: 31 patients (19 males; mean age 43.2 years) were recruited. Dental erosion was assessed using a modified version of Smith and Knight tooth wear index with scores from 0–5, the range depending upon the severity of the tooth wear. Two 2 channel pH catheters with 15 cm interval were bonded together to position the top sensor at 2 cm above the upper oesophageal sphincter and the lowest sensor at 5 cm above the lower oesophageal sphincter determined by manometry. The data of the middle two channels were used for artefact detection. Dental enamel demineralisation occurs at pH <5.5 so this was used to monitor pharyngeal pH as well as pH <4 as for GOR detection in the distal oesophagus. The results were compared with 7 controls without symptoms of reflux or dental erosion (5 males; mean age 22.6 years).

Results: In the distal oesophagus, there was no significant difference in % of reflux in the upright position ($p=0.097$) but significantly higher in the supine position ($p=0.017$) for patients when compared with controls. In the pharynx, there were no differences in both upright and supine positions in% time when pH <4 between controls and patients. However when analysed with pH <5.5 there were significantly higher percentage of time pH <5.5 in patients than controls in both upright ($p<0.001$) and supine (<0.001) positions. There were also significant relations between total tooth wear with % of pH <5.5 in score 3 ($p=0.04$) and score 4 ($p=0.04$) in the supine position.

Conclusion: In patients with suspected proximal reflux, supine GOR may play an important role in dental erosion. The long duration of pH between 4 and 5.5 in the pharynx, particularly in the supine position, may lead to increased chance of developing dental erosion in this group of patients, so pH threshold of <5.5 should be used for data analysis.

434 EIGHT YEARS EXPERIENCE OF 24 HOUR OESOPHAGEAL PH PAEDIATRIC STUDIES

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Purpose: Since 1 March 1995 the Royal Alexandra Hospital has performed 24 hour pH investigations in paediatrics and neonates, to look for the presence of gastro-oesophageal reflux disease. A literature search indicates few reports on the results of 24 hour pH investigations in paediatric patients. This paper describes the techniques used and the findings from a retrospective survey of the investigations.

Methods: The placement of the pH sensor above the lower oesophageal sphincter (LOS) is calculated using the Strobel Regression formula. This is checked by the use of a ''pull back'' technique that looks for a pH transition from the stomach into the oesophagus. Depending on patient age, a single or dual sensor catheter is used, which has an internal reference electrode. Flexilog3 recorder and software is used to record and analyse the results. Findings from the diary sheets are included in the report. The tests are reported on the total percentage time the sensors are exposed to acid below a pH of 4. Below 5% is reported as normal, between 5 and 10% borderline, and above 10% pathological.

Results: Medical Physics has received 411 referrals. 322 studies were concluded. 89 were not completed and of these 52 patients either cancelled or did not attend; in 31 patients it was not possible to pass the catheter, mainly due to severe anxiety; and 6 technical faults occurred. Of the studies completed 249 (77.3%) were normal, 41 (12.7%) were borderline, and 32 (9.9%) were pathological. The mean and median ages of the patients were 2.9 and 0.7 years. 203 studies were completed

on patients less than 12 months of age and 158 were less than 6 months old.

Conclusions: The relatively high number of normal results compared with pathological and borderline findings may be due to the significant number of patients less than 12 months of age. This may be related to their dietary intake of milk that acts as an acidity buffer.

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435 DOSE DEPENDENT ALTERATIONS IN HUMAN SWALLOWING PERFORMANCE FOLLOWING TOPICAL OROPHARYNGEAL ANAESTHESIA

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Background and Aims: Sensation is an essential component of the human swallowing mechanism; however, few data exist to delineate the role of sensation on swallowing behaviour. The aims of this study were to assess the relationship between swallowing function and removal of sensation by topical oropharyngeal anaesthesia and determine whether this is related to the level of sensory reduction.

Methods: Subjects were healthy adult volunteers (n = 20, 10 male, mean age 26 years). Swallowing performance was measured using the ''Wiles water swallow test'', which calculates both the time taken, and number of swallowing needed to drink 50 ml of water. Repeated swallowing measures were performed serially, before and up to 60 minutes after the application of topical lidocaine anaesthetic at doses of: 10, 20, and 40 mg and compared with placebo. Additionally, subjective sensation thresholds were recorded with electrical faucial pillar stimulation and with orange stick probe (by VAS).

Results: Compared with baseline (pre-anaethesia) and placebo measures, only the 40 mg dose of lidocaine altered swallowing. The main effect was immediately after anaesthesia, reducing both the speed of swallowing (7.89 (SD 2.34) *v* 10.11 (SD 3.26) ml/s, $p<0.05$) and increasing the interswallow interval (1.67 (SD 0.38) *v* 1.45 (SD 0.29) s, $p<0.01$). By 15 minutes, however, all measures had returned to baseline values. Lower doses of anaesthesia had no effect on swallowing measures, despite all doses producing a change in sensation thresholds immediately after application ($p<0.04$), which was maintained for 30 minutes with 20 and 40 mg.

Conclusions: Removal of sensation with topical anaesthesia adversely alters swallowing performance. Swallowing function is thus reliant on sensation, displaying an anaesthesia dose dependence, but this is not related to subjective sensory thresholds. These observations have relevance to how oropharyngeal anaesthesia is applied in the clinical setting, and shed light on the mechanism by which altered sensation affects swallowing physiology.

436 A TEMPORAL REPRODUCIBILITY STUDY OF TRANSCRANIAL MAGNETIC STIMULATION EVOKED ELECTROMYOGRAPHIC AMPLITUDES IN THE HUMAN OESOPHAGUS

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Background: Transcranial magnetic stimulation (TMS) allows study of the central motor pathways from cerebral cortex to muscles of the human pharynx and oesophagus and has been used to explore mechanisms of swallowing recovery from dysphagia after stroke. TMS thus holds promise as a potential clinical tool for predicating swallowing outcome in cerebral injury. However, TMS evoked EMG recordings from the GI tract pose unique challenges, which for clinical utility, need more rigorous evaluation. The aim of this study was to determine the reproducibility of TMS in evoking responses in the oesophagus.

Methods: EMG was recorded via an intraluminal catheter from the proximal striated muscle oesophagus in response to TMS in 8 healthy subjects. For 6 different stimulus intensities (SI) (range 5% below motor threshold (MT) to 20% above), 20 consecutive TMS stimuli were delivered over a single scalp point at 5 second intervals across 3 time points, 40 minutes apart. The amplitudes for each EMG response were measured and the means sequentially calculated for each SI and then log transformed. The repeatability coefficients (RC) for the 3 time points were then calculated for each SI for the 20 means and presented as an exponential ratio.

Results: TMS was well tolerated, and oesophageal EMG responses were easily recorded from all subjects. At 5% below MT, an optimal RC of 2 was achieved after 15 stimuli. A higher number of stimuli did not yield further improvement in repeatability. For all other SI this level of optimisation was achieved at between 5 and 10 stimuli. For all SI the largest reduction in RC was achieved over the first few stimuli.

Conclusion: An optimal RC of 2 can be achieved for oesophageal TMS if 15 stimuli are applied at 5% below MT and between 5 and 10 for all other SI above this. As the RC is an exponential ratio this implies that any change in magnitude over time elicited of less than double falls within the physiological limits of variability. Thus, given these parameters, TMS can be used reliably in future studies of patients with dysphagia after brain injury

437 CORTICAL PROCESSING OF NOXIOUS VISCERAL AND SOMATIC STIMULATION

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Background and Aims: Visceral and somatic pain perceptions differ in key aspects: poor localisation of visceral pain and its ability to be referred to somatic structures. It is known that visceral afferents diverge at the spinal level, often then converging with somatic afferents. Whether these mechanisms are sufficient to explain the differences, or whether visceral pain activates different cortical regions is not fully understood.

Methods: Eight healthy right handed subjects (mean age 30.0 (SD 2.17) years) were recruited for the study. Each subject was scanned in a 3-Tesla magnet. They received either thermal stimuli (via a 2×1 cm thermal resistor) to the left foot or midline back or rectal balloon distension via a 2 cm latex balloon). The stimuli were matched for their level of unpleasantness at a rating of 4 out of 10. Echo planar imaging was used for the functional scans and 3D Turbo FLASH scans obtained for high resolution brain scans. Images were analysed with FEAT.

Results: The ratings of the stimuli matched for unpleasantness. The intensity of the visceral stimulus was significantly lower than the two somatic groups. A bilateral network of cortical regions was activated including the thalamus, secondary somatosensory cortex, insula, and mid cingulate cortices bilaterally. On region of interest analysis, there were no significant differences in cortical activation between the somatic and visceral groups in any of the above regions.

Conclusion: Visceral and somatic noxious stimulation, matched for unpleasantness, result in a similar bilateral cortical network of activation: the ''pain matrix''. This supports the hypothesis that the ascending spinal characteristics of visceral afferents are the cause of the differences in somatic and visceral pain perception.

438 ALTERATIONS IN HUMAN SWALLOWING PERFORMANCE ARE CORRELATED WITH SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background and Aims: It is recognised that swallowing and respiration are intimately related; however few data exist on the relation between swallowing function and respiratory disorders. The aim of this study was to explore the interaction between swallowing performance and clinical respiratory dysfunction in a population of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).

Methods: COPD patients (n = 27, 15 males, mean age 74 yrs), admitted with acute exacerbation were consecutively recruited from Hope Hospital. A water swallow test was used to assess swallowing performance. Instructions were to drink 50 ml of water ''as quickly and comfortably as possible'', while the time and number of swallows taken was recorded. For each patient 3 measurements were taken and used to calculate mean swallowing velocity (ml/s) and swallow capacity (ml). Swallowing measures were correlated with peak flow recordings (PEFR) and oxygen saturation levels (O_2 Sat). Patients were also followed up every other day until discharge.

Results: Compared with healthy (age matched) controls, swallowing was slower in COPD patients being more pronounced in males (14.6

(SD 5.9) *v* 10.6 (SD 5.6) ml/s, $p<0.04$). There was a clear correlation between peak flow and swallowing velocity amongst patients on admission with slower swallowing velocities being associated with lower PEFR (correlation coefficient (r) = 0.52, $p<0.01$). However, no differences in swallowing capacity were observed and swallowing performance was not correlated with O_2 Sat. Over the following 2 weeks, there was some normalisation of swallowing performance with COPD recovery.

Conclusions: COPD effects swallowing by reducing its velocity. The greater the severity of COPD, the slower the velocity. Although normalisation does occur during convalescence, clinicians should be aware that COPD can alter swallowing function, predisposing patients to aspiration. Thus, greater vigilance of swallowing dysfunction in COPD should be considered.

439 CYCLO-OXYGENASE 2 DOES NOT CONTRIBUTE TO THE DEVELOPMENT OF ACID INDUCED HUMAN VISCERAL PAIN HYPERSENSITIVITY

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Introduction: Increased spinal cord neuronal excitability i.e. central sensitisation (CS), contributes to the development and maintenance of visceral pain hypersensitivity.[1] Cyclo-oxygenase 2 (COX-2) is constitutively expressed in the spinal cord, is rapidly upregulated following inflammation and contributes to CS in somatic pain hypersensitivity via prostaglandin production.[2] However, its role in mediating visceral pain hypersensitivity is unknown.

Aim: To determine if Valdecoxib (a selective COX-2 inhibitor) attenuates the development of CS in our human model of oesophageal acidification induced hypersensitivity.[3]

Methods: 10 healthy subjects were studied in a randomised, double blind, placebo controlled, crossover study. Pain thresholds (PT) to electrical stimulation were determined in the proximal oesophagus (PO) and foot (somatic control) before and after a 30 minute distal oesophageal infusion of 0.15M HCl acid. Valdecoxib (40 mg), or placebo was given orally for 4 days prior to the acid infusion and PT measured for the following 120 minutes post acid.

Results: There was no effect of Valdecoxib on baseline PT in the PO ($p=0.8$), or foot ($p=0.4$). Valdecoxib did not attenuate the reduction in PT in the PO which is induced by a distal acid infusion (AUC: −149 (SD 79) Valdecoxib, −178 (SD 116), placebo, $p=0.71$). Valdecoxib had no effect on foot PT following acid (AUC: $p=0.8$). No side effects were noted on either visit.

Conclusions: Valdecoxib was not analgesic (baseline pain thresholds were unchanged on both visits). Pretreatment with Valdecoxib did not prevent the development of acid induced visceral pain hypersensitivity, or lessen its magnitude. This suggests that constitutive spinal COX-2 does not contribute to the initial development of visceral CS. However, COX-2 induction may occur several hours after the onset of inflammation and may therefore contribute to the maintenance of CS. Studies using COX-2 inhibitors to ascertain their role in established CS in visceral hypersensitivity states are therefore warranted.

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2. Seybould, *et al. Pain* 2003;**105**:47–55.
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440 LONG TERM OUTCOME OF PNEUMATIC DILATATION IN ACHALASIA

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Background: Pneumatic dilatation (PD) has been shown to be effective for treatment of achalasia in the short and medium term. However, there is limited information on the long term outcome of pneumatic dilatation in achalasia.

Aims: To evaluate the clinical status and quality of life of achalasia patients treated with PD more than 6 years ago.

Methods: All achalasia patients treated with PD between 1992 and 1996 were identified and their records reviewed. A postal questionnaire assessing symptoms of achalasia was sent to all patients. For each symptom of dysphagia, regurgitation, chest pain, and heartburn, the frequency and severity were assessed resulting in a score range of 0 to 20. Patients also rated their overall symptomatic status compared to before PD on a categorical scale (better, same or worse). Patients then completed the Short Form-36 (SF-36) questionnaire to assess their quality of life. Mean SF-36 scores were compared to those of the Western Australian population using independent samples *t* test.

Results: Forty nine patients had PD between 1992 and 1996. Mean length of follow up from PD was 8.4 years (range 6.3 to 10.6 years). Eight (16%) patients had died of unrelated causes. Four (8%) patients had myotomy and one (2%) had botulinum toxin injection for recurrent symptoms following PD. Twenty three of the 36 (64%) patients who had PD as sole treatment for achalasia completed the symptom and SF-36 questionnaires. Median (IQR) of dysphagia, regurgitation, chest pain and heartburn scores were 2 (0–6), 1 (0–6), 0 (0–4), and 2 (1–8) respectively. Nineteen of these 23 (83%) patients reported overall symptomatic improvement following PD. Mean SF-36 scores for the subscales of general health (62.5 *v* 75.8, $p=0.001$), social function (61.7 *v* 89.8, $p<0.0001$) and mental health (69.0 *v* 79.9, $p=0.001$) were significantly lower than those of the Western Australian population.

Conclusions: Achalasia patients treated with PD have adequate control of symptoms in the long term. However, there is some impairment of quality of life of achalasia patients treated with PD.

441 CAN ELECTROGASTROGRAPHY REPLACE GASTRIC EMPTYING FOR CHILDREN WITH GASTRIC DYSFUNCTION?

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Background: Children with abdominal pain, vomiting, and/or bloating often have gastric dysfunction such as delayed gastric emptying (GE). GE studies on children are difficult to perform due to the necessity of radioisotopes where gamma scintigraphy is utilised and the long duration of measurement even when electrical impedance tomography (EIT) is used. In addition, symptomatic children often have small appetites or vomit during measurement. Electrogastrography (EGG) measures gastric slow waves and is practically easy to carry out. We have performed EGG and GE on children to evaluate whether EGG might replace GE as a measure of delayed gastric transit.

Method: Ten children (median age 10 yrs, range 3–15 yrs) with abdominal pain (n = 9), vomiting (n = 5), and/or bloating (n = 4) underwent EGG and GE studies. The EGG signal was recorded using a portable digitizer (Digitrapper-EGG, Medtronic, Sweden). The EGG data were analysed by dedicated software (Polygraph, Medtronic, Sweden) and dominant frequency of 2.5–3.5 cpm was regarded as normal. GE was performed using EIT (DAS-01P, Sheffield University). A cup of porridge was used as a test meal.

Results: Seven children had abnormal EGG (significant bradygastria >60%) and 3 had normal EGG. Of those 7 children with abnormal EGG, 5 also had delayed gastric emptying ($t1/2 >110$ minutes). Of the 3 children with normal EGG, all 3 had normal GE.

Conclusion: In this study, EGG results have matched gastric emptying results in a high proportion of children (8 out of 10). This suggests that EGG could be used to predict gastric stasis in children where GE measurement is not possible.

442 APPLICABILITY OF SYMPTOM BASED DIAGNOSTIC CRITERIA TO PATIENTS WITH A FIRM DIAGNOSIS OF IBS MADE IN THE OUTPATIENT CLINIC SETTING

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Background and Aim: Diagnosis of irritable bowel syndrome (IBS) relies on the use of symptom based criteria, as there is no biological marker for the disease. Despite widespread use of these criteria in the research setting, and recognition that they are highly specific,[1] virtually nothing is known regarding the sensitivity of the current Rome criteria in clinical practice and epidemiological surveys have suggested that they may be too restrictive for routine clinical use.[2] The aim of this study was to assess the sensitivity of the three commonly used criteria (Manning, Rome I, and the currently recommended Rome II) in patients who had been followed up for at least one year after having been given a firm clinical diagnosis of IBS by an experienced physician with an interest in the condition.

Methods: A questionnaire detailing symptoms was given to 100 consecutive IBS patients attending a university hospital outpatients clinic.

Results: Of the 100 patients, 56 of whom were female, 94 (94%) satisfied Manning criteria (difference from Rome II: $p<0.01$), 82 (82%) satisfied Rome I criteria ($p<0.05$), and 73 (73%) satisfied Rome II criteria. Using Rome II criteria excluded 23 Manning positive cases and 13 cases who were Rome I positive. Two patients who were Rome II positive were Manning negative, and 4 were Rome I negative. 67 (67%)

of patients with a clinical diagnosis of IBS met all three criteria but only 4 (4%) of IBS patients failed to meet any.

Conclusions: The longest standing diagnostic criteria (Manning), which were developed specifically for clinical use, remain the most sensitive in clinical practice. The Rome criteria are known to be specific, but this appears to be at the expense of sensitivity. Thus in order to avoid unnecessary investigations it is important to be cognisant of the fact that failure of a patient to meet these strict modern diagnostic criteria does not preclude a clinical diagnosis of IBS.

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2. Boyce PM, *et al. Am J Gastroenterol* 2000.

443 RELATION OF ABDOMINAL BLOATING TO PHYSICAL DISTENSION IN IRRITABLE BOWEL SYNDROME: EFFECT OF BOWEL HABIT

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Introduction: We have recently developed and validated the technique of Abdominal Inductance Plethysmography to objectively measure abdominal girth[1] and have shown that subjective worsening of abdominal bloating (AB) through the course of the day is associated with an objective increase in abdominal girth/distension (AG) in patients with irritable bowel syndrome (IBS).[2]

Aim: To determine whether bowel habit influences the nature of AB and its relationship to AG in patients with IBS.

Methods: AG was recorded for 24 hours in 19 diarrhoea predominant IBS (d-IBS) (aged 25–59 yrs) and 14 constipation predominant IBS (c-IBS) (aged 18–73 yrs) patients (Rome II) and compared with 18 healthy volunteers (aged 18–67 yrs). AB was scored on a 0–3 scale (3 = severe).

Results: AB worsened to a similar degree in both patients with c-IBS (2.3 (1.8 to 2.8); mean (95% CI)) and d-IBS (2.1 (1.6 to 2.5)) compared with controls (0.4 (0.1 to 0.6); $p<0.001$). Likewise, AG increased by a similar amount in both patients with c-IBS (+4.6 cm (1.2 to 8.0) cm) and d-IBS (+3.1 cm (0 to 6.2) cm) compared with controls (−0.7 cm (−3.3 to 2.0)cm: $p=0.02$, $p=0.06$, respectively). Interestingly however, these objective changes in AG only correlated with subjective AB in the c-IBS ($r=0.61$; $p=0.02$) and not the d-IBS ($r=0.02$; $p=0.9$) patients.

Conclusions: Both c- and d-IBS patients bloat and distend more than controls but to similar extents. However, whereas AB is directly related to physical changes in AG in c-IBS, this relationship appears more complex in d-IBS and this might be due to the greater prevalence of visceral hypersensitivity reported in this group.

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444 ARE PATIENTS WITH IBS MORE LIKELY TO SEEK A PHYSICAL RATHER THAN A PSYCHOLOGICAL EXPLANATION FOR UNEXPLAINED SYMPTOMS?

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Aims: A tendency to attribute unexplained symptoms to physical disorders is thought to be common in patients with irritable bowel syndrome (IBS). We tested this hypothesis by assessing symptom severity, symptom interpretation, and quality of life in patients attending a hospital gastroenterology clinic.

Method: Patients referred to hospital gastroenterology clinics were recruited prospectively and invited to return self completed, validated questionnaires comprising the Medical Outcome Survey (Quality of Life QOL SF-36), the IBS Symptom Severity Score (IBS SSS) and the Symptom Interpretation Questionnaire (SIQ), a measure of the tendency to interpret unexplained symptoms as a physical disorder (somatising style), an emotional response to stress (psychologising style) or a normal experience (normalising style). The diagnosis of IBS was based on the Rome II criteria after case record analysis. Controls comprised GI patients with non-IBS diagnoses.

Results: 102 patients (M:F 41:61) returned completed questionnaires (65% return rate). QOL scores in IBS patients (n = 32, M:F 9:23) were not statistically different from those of non-IBS patients (n = 70, M:F 32:38). In both patient groups, the normalising style of symptom interpretation predominated, with no excess of somatising style in the IBS group. In both patient groups, the psychologising style correlated with impaired QOL in the mental health domains (Spearman's correlation −0.42, $p<0.05$). In IBS patients, the severity of abdominal pain correlated with the psychologising style (Spearman's correlation 0.47, $p<0.05$).

Conclusions: Symptom interpretation does not differ between IBS and non-IBS patients. However, in IBS patients, there is a correlation between the severity of abdominal pain and the tendency to seek a psychological explanation for physical symptoms.

445 RISK FACTORS FOR IRRITABLE BOWEL SYNDROME: A COMMUNITY STUDY

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Background: Irritable bowel syndrome (IBS) is very common, impairs patients' quality of life, and is associated with substantial cost implications for the NHS. Multiple factors have been implicated in the pathophysiology but its aetiology remains poorly understood. We have examined the prevalence of IBS and potential risk factors in the local community.

Methods: A validated questionnaire was sent to 4000 community subjects over the age of 18, stratified by age, sex, and ethnicity to be representative of the Sandwell population at the 2001 census. IBS was defined by the Rome II criteria as at least 12 weeks of abdominal pain/discomfort in the preceding year with two of: relief with defaecation/change in bowel frequency with pain/change in bowel consistency with pain.

Results: 2231 subjects responded (59%). 691 (18%) refused to participate and 6 were incomplete. 1534 (41%) were evaluable (634 male, mean age 50 (SD 16) (range 20–80) years). Non-responders were more likely to be male and younger ($p<0.0001$). Univariate analysis suggested younger age, smoking, gastro-oesophageal reflux disease (GORD) symptoms, anticholinergic drug use (all $p<0.0001$), female sex ($p=0.002$), excess alcohol consumption ($p=0.01$), antidepressant use ($p=0.006$), and no educational attainment ($p=0.04$) were associated with IBS. Multivariate forward stepwise logistic regression analysis revealed (see table).

Conclusions: Younger age, GORD symptoms, anticholinergic drug use, female sex, and smoking are independently associated with IBS in community subjects.

Abstract 445

Factor	OR (95% CI)	p Value
Age	0.98 (0.97 to 0.99)	<0.0001
GORD symptoms	3.95 (2.93 to 5.33)	<0.0001
Anticholinergic drugs	4.08 (2.20 to 7.58)	<0.0001
Female	1.54 (1.14 to 2.08)	0.005
Smoking	1.50 (1.08 to 2.10)	0.02

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446 E-CADHERIN EXPRESSION DOES NOT APPEAR TO BE MODULATED BY TNF-α IN AN EX VIVO MODEL OF BARRETT'S METAPLASIA

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Introduction: The majority of oesophageal adenocarcinoma arises from Barrett's metaplasia (BM) following a metaplasia-dysplasia-carcinoma sequence. E-cadherin expression is down regulated along this progression, and TNF alpha (TNF-α) expression is increased. We have demonstrated in a cell culture model that TNF-α stimulation results in down regulation of E-cadherin mRNA, but that protein expression is unchanged ex vivo. We aim to investigate the modulation of E-cadherin mRNA by TNF-α in an ex vivo tissue culture model.

Methods: Specimens of Barrett's metaplasia and matched normal squamous (SQ) and duodenal (D) epithelium were cultured by standard tissue explant methods for 18 hours with or without TNF-α at 50, 200, and 500 ng/ml (n = 12, 6, and 7). A further seven sets of biopsies were

cultured for 3 hours with or without TNF-α at 200 ng/ml. Tissue viability was confirmed by LDH assay of the culture media. At the end of the culture period mRNA was extracted and E-cadherin expression assessed by Real Time PCR and expressed as a fold change compared to unstimulated cultured tissue. Results were compared using Wilcoxon Signed Rank Test and one way ANOVA.

Results: At 18 hours there was a trend to increased E-cadherin expression in SQ tissue and decreased expression in BM tissue. This was noted only with 200 ng/ml of TNF-α. No changes were seen in duodenal tissue. Short term culture showed some evidence of down regulation in SQ and BM tissue but not duodenal. All median values fell between 0.5 and 2 fold difference and no result was statistically significant.

Conclusion: Our results fail to show a significant modulation of E-cadherin mRNA expression by TNF-α in an ex vivo model, although the numbers are small and it is possible we may have missed a small effect. However the role of TNF-α in BM remains elusive and may not be due to alteration of cell to cell adhesion.

447 LONG TERM CHRONIC *HELICOBACTER PYLORI* INFECTION UPREGULATES GASTRIC EGFR, C-MET, ADAM 17, AND COX-2 EXPRESSION IN THE MONGOLIAN GERBIL

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Introduction: *H pylori* activates the epidermal growth factor receptor (EGFR) and c-Met in gastric epithelial cells in vitro. EGFR activation is dependent on extracellular transmembrane metalloprotease cleavage of EGFR ligands. Long term *H pylori* infection in the Mongolian gerbil results in gastric cancer. The aims of this study were to examine the effects of long term *H pylori* infection in the Mongolian gerbil on gastric expression of the tyrosine kinase receptors EGFR and c-Met, and of membrane metalloprotease ADAM 17 and COX-2.

Methods: Male Mongolian gerbils were orally infected with *H pylori* SS1 strain. Infected gerbils (n = 7) and controls (n = 9) were sacrificed at 62 weeks post infection (PI). Gastric mucosa was processed for culture, histology, and snap frozen for RT-PCR analysis. Cross-species PCR and sequencing were used to identify gerbil transcripts for EGFR, c-MET, ADAM 17, and COX-2. The ratio of transcripts to β-actin was determined by computer image analysis.

Results: All infected gerbils had some degree of chronic gastritis, with 86% having pan gastritis by 62 weeks. *H pylori* infection resulted in significantly increased gastric expression of both EGFR (EGFR: β-actin ratio 2.53 (SD 0.22), $p<0.02$) and c-Met (0.44 (SD 0.06), $p<0.05$) compared with uninfected controls (EGFR 1.11 (SD 0.20); c-Met 0.19 (SD 0.38)). The gastric expression of ADAM 17, a potential membrane metalloprotease involved in EGFR transactivation, was also significantly increased in *H pylori* infected gerbils (1.1 (SD 0.15) *v* 0.59 (SD 0.11), $p<0.02$) as well as expression of COX-2 (0.74 (SD 0.81) *v* 0.41 (SD 0.07), $p<0.01$).

Conclusions: Long term *H pylori* infection in gerbils results in increased gastric expression of EGFR and c-Met receptors which are known to be activated by *H pylori* in vitro. In addition, ADAM 17 and COX-2 transcripts are significantly increased. Over expression of these genes in *H pylori* infection may be relevant for the epithelial hyperproliferation and reduced apoptosis observed in the model.

448 DELAYS IN PRESENTATION AND DIAGNOSIS OF PATIENTS WITH OESOPHAGEAL AND GASTRIC CANCER IN SCOTLAND

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Introduction: Delays in presentation of symptoms, attaining diagnosis, and initiation of treatment may adversely affect outcome in patients with oesophageal and gastric cancer. This study sought to identify contributory factors to such delays.

Method: The Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) conducted a prospective population based audit of all oesophageal and gastric cancers in Scotland from July 1997 to July 1999. Predetermined outcome parameters included time from onset of symptoms to seeking medical attention and time from attending to establishing a diagnosis.

Results: 33.1% of 3292 patients delayed more than 4 months in seeking medical attention. There was no significant difference between tumour location (32.5%, 36%, and 32.7% for oesophageal, junctional, and gastric cancers, respectively), size of hospital, geographical location, or deprivation quintile of patients. 22.2% of patients were delayed more than 4 weeks before a diagnosis was established and 2.3% more than 4 months. This was independent of tumour location and deprivation quintile. However, there were significant differences between health boards (range 13.2% to 31.6% ($p<0.001$)) and size of hospital. Of 53 hospitals studied, delays beyond 4 weeks in those receiving fewer than 10 cases annually was 13.4% compared with 25.2% in those receiving 35 to 74 cases annually ($p<0.001$).

Conclusion: Community based education and guidelines have been introduced to heighten patient awareness of upper gastrointestinal symptoms. However a greater impact in facilitating a rapid diagnosis, thereby reducing target times to treatment, may be achieved by minimising system delays in the processing of patients with oesophageal and gastric cancers.

449 INFLUENCE OF DEGREE OF SURGICAL RESECTION ON THE MORBIDITY AND MORTALITY OF GASTRIC CANCER

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Introduction: Surgical Resection of gastric cancers remains the standard treatment for patients with localised disease. We investigated how the degree of surgical resection influenced postoperative morbidity and mortality.

Methods: Data were extracted from the Scottish Audit of Gastric and Oesophageal Cancer (SAGOC), a prospective population based audit of all oesophageal and gastric cancers in Scotland. Test of association used the χ^2 statistic.

Results: Of 1264 patients diagnosed with gastric cancer, 646 patients had an operative procedure, with 475 patients undergoing resection—distal gastrectomy (DG) n = 272 and total gastrectomy (TG) n = 168. The commonest complications following resection included chest infections 11% *v* 18.5% ($p<0.05$), cardiac complications 7.7% *v* 7.7% and anastomotic leaks 2.2% *v* 14.3% ($p<0.05$) in DG and TG patients, respectively. The in hospital mortality was 46% for patients who developed an anastomotic leak irrespective of the procedure.

For all resections carried out for gastric and oesophageal cancer, the removal of contiguous organs resulted in significantly increased mortality and decreased one year survival. It is important to note the resection of contiguous organs was more commonly associated with gastric surgery.

Conclusion: The data illustrate the increased morbidity and mortality associated with the increased radical nature of surgery for gastric cancer. As such more radical resections need to be justified with better long term survival.

Abstract 449

Organ removal	Cases (n)	Mortality (%)	1 year survival (range)
Spleen	131	24 (18.3)	50.9 (42.2–59.6)
Pancreas	30	7 (23.3)	38.1 (21.4–56.8)
Liver	5	2 (40)	20.0 (0–55.1)

450 ASSESSMENT OF THE VALUE OF STAGING LAPAROSCOPY COMPARED WITH STAGING COMPUTED TOMOGRAPHY IN PATIENTS WITH UPPER GASTROINTESTINAL MALIGNANCY

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Introduction: Resection offers the only chance of cure to patients with upper gastrointestinal malignancy. Staging is essential to select patients who will benefit from operation. The aim of this study was to assess the benefit of staging laparoscopy, compared with staging CT, for staging patients with upper gastrointestinal malignancy.

Methods: Fifty five consecutive patients from a single institution with oesophageal, gastro-oesophageal junction, and gastric malignancy underwent preoperative staging by laparoscopy and CT between

January 2002 and August 2003. Data pertaining to staging investigations were recorded prospectively.

Results: Thirty three patients (60%) underwent a resection. Six patients (10.9%) were found to have metastatic disease following CT and underwent palliation. In fourteen (25.5%) patients, laparoscopy revealed carcinomatosis and/or multiple hepatic metastases undetected by CT, so laparotomy was not performed. Four patients (7.27%) were found to be inoperable at laparotomy had normal CT and laparoscopic findings. As regards detection of local and distant metastasis, laparoscopy showed a sensitivity of 92.7%, significantly higher than CT staging (74.5%; $p<0.05$, Z test for 2 proportions/two tailed test). Complications and port site metastases were seen in 3% and 1.8% of patients, respectively.

Conclusions: Laparoscopic staging is recommended in patients with upper gastro-intestinal malignancy, as it may prevent unnecessary laparotomy in a proportion of CT staged patients presumed to have resectable malignancy and the risks of complications and port site metastasis appear low.

451 SOCIOECONOMIC DEPRIVATION IS ASSOCIATED WITH DIAGNOSTIC DELAY AND POOR OUTCOMES IN PATIENTS WITH GASTRIC CANCER

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Aims: To examine trends in diagnostic delays, stages of disease, and outcomes for patients with gastric cancer in relation to (1) socioeconomic deprivation and (2) the introduction in 1999 of all Wales minimum standards that set maximum waiting times for gastroscopy.

Methods: Three hundred consecutive patients presenting with gastric cancer between 1995 and 2003 were studied prospectively. Multiple Indices of Deprivation (MID) for electoral divisions as described by the Office of National Statistics were used to measure socioeconomic deprivation. Patients were ranked into quintiles, and patients in the upper quintile (highest deprivation scores: MID >40, n=46) were compared with patients in the lower 4 quintiles.

Results: Diagnostic delay in patients with MID <40 fell from a median of 15 weeks in the late 1990s to 10 weeks in the early 2000s ($p=0.02$). In contrast, delays for patients with MID >40 increased from 24 to 28 weeks ($p=0.99$). Since 1999 gastric cancer patients with MID >40 have been more likely to be diagnosed with stage IV inoperable cancers (60%) than patients with MID <40 (38%, $p=0.102$). The R0 resection rate for patients with MID <10 (n=71) remained comparable at between 45% and 36%, whereas this rate fell significantly in patients with MID >40 from 47% to 4% ($p=0.01$). Five year survival in patients with MID <10 improved from 15% to 40% ($p=0.13$), whereas survival for patients with MID >40 fell from 15% to 6% ($p=0.05$).

Conclusion: Since the introduction of minimum standards diagnostic delays are reducing and outcomes are improving for socioeconomically advantaged patients with gastric cancer. By contrast, delays have lengthened and outcomes have worsened for patients with the highest MID scores. Healthcare planners should take such data into account when making decisions on cancer services and resource allocation.

452 DYSPHAGIA: PREDICTORS FOR MALIGNANCY AT ENDOSCOPY

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Background and Aims: Current guidelines recommend urgent (within 10 days of referral) endoscopic investigation in patients presenting with dysphagia at any age. We studied the incidence of significant upper GI pathology in patients presenting with dysphagia with a view to identify variables which may predict the presence of upper GI malignancy in this group of patients.

Methods: A retrospective analysis was carried out on all patients who underwent upper GI endoscopy for dysphagia over a 2 year period (1 April 2000–31 March 2002). Histological reports of all biopsies taken at endoscopy were obtained and reports of patients who subsequently had a barium meal were studied to obtain the final diagnosis.

Results: 260 patients (113 males and 147 females) had endoscopy for dysphagia. Of these 14 had associated weight loss, 10 had anaemia, and 35 had reflux symptoms at the time of referral. 73 (28%) patients had normal or insignificant findings. We found that significantly more females (54) presented with dysphagia and had normal or insignificant findings compared with males (19). 40 (15.3%) patients (36 oesophageal and 4 gastric; 28 male and 12 female) had malignancy confirmed by histology. Acid related causes such as oesophagitis, Barrett's, and peptic stricture were found in 66 (34.2%) patients. 18 (7%) had motility disorders and 41 (15.7%) had other causes explaining their dysphagia. 10 patients were aged less than 45 years and there were no GI cancers. 35 patients were aged 46–55 years and 3 of them had oesophageal cancer. 28.5% of patients presenting with associated weight loss had upper GI cancer as opposed to 2.8% in patients with associated reflux, 10% in patients with anaemia, and 11.6% in the dysphagia only group.

Conclusion: Our data show that in patients presenting with dysphagia, male sex, age above 45 years, and associated weight loss are high risk predictors of upper GI malignancy. We conclude that all patients, regardless of the age presenting with dysphagia, should undergo endoscopy to identify significant and treatable upper GI pathology. However whether this should be performed on an urgent basis in patients less than 45 years without associated symptoms is debatable.

453 MULTIDISCIPLINARY TEAMS INCREASE REFERRAL RATES AND IMPROVE OUTCOMES OF TREATMENT FOR OESOPHAGOGASTRIC CANCER

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Background: Despite the key recommendations of the NHS Executive that multiprofessional teams should treat patients with oesophagogastric cancer, little evidence has been identified regarding the effectiveness of team working in upper gastrointestinal cancer management.

Aims: To compare outcomes for patients diagnosed with oesophagogastric cancer and managed by a multidisciplinary team (MDT0 (two consultant surgeons, specialist radiological support, and neoadjuvant chemoradiotherapy where indicated), with outcomes of patients managed by clinicians independently prior to the inception of a MDT in a large UK cancer unit.

Methods: 1227 consecutive patients with oesophagogastric cancer were studied between 1 January 1991 and 31 December 2002. The outcomes of the 593 patients diagnosed prior to the introduction on a MDT were compared with the outcomes of the 634 patients managed by the MDT.

Results: See table.

Conclusion: MDT management increased referral rates almost threefold, reduced operative mortality fourfold and improved survival fivefold. The results underscore the impact of multiprofessional teams in refining preoperative diagnoses and stage, optimal case selection, and peri-operative care for patients with oesophagogastric cancer.

Abstract 453

	Oesophagus		Stomach cancer	
	Pre	Post MDT	Pre	Post MDT
No. diagnosed/yr	46	49	64	56
Surg. referral (%)	23*	54*	22*	65*
R0 resection (%)	15	20	16	21
Op. mortality (%)	24†	6.7†	12	8.3
5 yr survival (%)	9‡	45‡	11*	56*

*$p<0.001$; †$p=0.01$; ‡$p=0.002$.

454 RANDOMISED CONTROL TRIAL OF AUDIO TAPE RECORDING TO ENHANCE OESOPHAGOGASTRIC CANCER CONSULTATIONS

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Background: Consultations to convey a diagnosis of oesophagogastric cancer may be difficult and traumatic for patients and as many as 50% of patients are displeased with the information given to them by their doctors.

Aims: The aim of this study was to assess the value of tape recording this consultation, to determine whether this might enhance patients' memory of key facts, and reduce anxiety before treatment.

Methods: Fifty patients were allocated at random (stratified for sex) to have their consultations audio taped or not. Twenty six patients received taped consultations (median age 66 years, 17 m, 9 oesophageal, 17 gastric cancers) and were compared with 24 control patients (69 years,

19 m, 11 oesophageal, 13 gastric) who did not. All patients completed a hospital anxiety and depression (HAD) questionnaire and were re-interviewed one to two weeks later.

Results: Twenty four patients listened to their tapes (2 elected not to). Patients who had received taped consultations were less likely to forget key facts regarding their diagnosis and treatment options (0 of 26 patients) compared with patients who had not received a tape (8 of 24 patients, $\chi^2 = 10.3$, DF 1, $p = 0.001$). HAD A scores were similar in both groups (tape 6 (2–10), no tape 6 (0–21)). HAD D scores were lower in patients who had received a tape (2.5 (0–23)) compared with patients who had not (4 (0–10), $p = 0.891$). Whether or not patients received a tape did not influence the surgical resection rate (tape 55% *v* no tape 50%, χ^2 0.105, DF 1, $p = 1.0$).

Conclusion: All of the patients who listened to the tape found it helpful, and in broad terms, tape recorded interviews had a positive effect on the ability of patients and their families to participate in management decisions.

455 HAS THE IMPLEMENTATION OF THE TWO WEEK RULE IMPACTED ON MORTALITY IN UPPER GI CANCERS? AN AUDIT AT TWO DISTRICT GENERAL HOSPITALS

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Introduction: The two week wait standard for upper GI cancers was introduced on 1 July 2000 and requires patients to be seen by a specialist within 2 weeks of referral. British Society of Gastroenterology guidelines on management of oesophageal and gastric cancer (published May 2002) emphasised that there were few data to suggest that a referral within 2 weeks would improve outcome quantitatively. Our aim was to determine if the implementation of the two week rule had made any significant impact on mortality in upper GI cancers.

Methods: Identified patients with upper GI cancers from the cancer databases at Oldham Hospital and Rochdale Infirmary. Reviewed medical records of patients diagnosed between January 1999 and December 2001, i.e. 18 months before and 18 months after introduction of two week rule.

Results: 279 cases were identified. 146 (102 M, 44 F) were oesophageal cancers of which 70 were diagnosed before the two week rule and 76 after. 133 cases (81 M, 52 F) of gastric cancer were reviewed, with 65 occurring before the two week criteria and 68 after. 31% of patients were diagnosed after being admitted on the acute take, 30% had been referred on an urgent outpatient's basis, and 16 patients (11%) were diagnosed via the two week referral. 44 patients (33%) in the group prior to the two week implementation had metastases compared with 49 (34%) in the post implementation group. There was no significant difference in treatment modalities administered to both groups.

Conclusions: The two week rule has not led to any significant improvement in 12 or 18 month mortality in upper GI cancers.

456 A LARGE DISTRICT GENERAL HOSPITAL CAN PROVIDE ACCEPTABLE MANAGEMENT OF UPPER GI CANCER

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Introduction: Upper gastrointestinal (UGI) cancer is the third most common cause of cancer deaths in the UK. It is associated with a poor prognosis with a 75% mortality rate at 1 year. A typical district general hospital (DGH) serving 200 000 patients would expect to diagnose 75–100 UGI cancers per year, levels now considered too low to ensure continued surgical expertise. To improve these trends, the NHS executive issued revised COG guidelines in 2001 which recommended the establishment of specialist treatment teams within centralised cancer centres serving populations of 1 to 4 million. We present our experience from a three year period in a large DGH (population 400 000), showing that we are able to offer the expected level of care.

Methods: A prospective audit was carried out of all UGI cancers diagnosed between January 2000 and December 2002. All cases were discussed at a specialist multidisciplinary team meeting (including UGI surgeons, gastroenterologist, UGI oncologist, radiologist, and histopathologist). Two experienced surgeons performed all surgical procedures. Surgical outcomes including 30 day mortality, 1 year survival, and readmission rates were analysed per anatomical subgroup.

Results: 250 gastric, 229 oesophageal, and 149 pancreatobiliary cancers were diagnosed. 92 proceeded to planned curative surgical resection. The outcomes per subgroup were: Gastric (n = 42), 30 day mortality 4.8%; 1 year survival 66.7%; 30 day readmission rate 21.4%. Oesophageal (n = 42), 30 day mortality 11.9%; 1 year survival 57.1%; 30 day readmission rate 17.9%. Pancreatobiliary (n = 8), 30 day mortality 0%, 1 year survival 87.5%; 30 day readmission rate 0%.

Conclusions: A large DGH with a service population of 400 000 may gain sufficient exposure to UGI cancer to ensure adequate surgical expertise in this field with acceptable surgical outcomes. The provision of a specialist multidisciplinary team ensures the appropriateness of treatment and provides the resource for clinical audit. The provision of these services locally ensures high quality treatment without increasing the burden on overstretched central resources.

457 TWO WEEK CANCER GUIDELINES: INCREASED WORKLOAD FOR NO ADDED BENEFIT?

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The NHS cancer plan advocates all patients felt by their general practitioner (GP) to have symptoms suggesting cancer be seen by a specialist within two weeks of referral, that is the ''two week cancer guideline'' (TWG). Before implementing this policy, the gastrointestinal (GI) physicians at our institution allocated priorities for clinics or ''direct'' endoscopy procedures depending on symptoms described in the GP referral letter—that is, consultant allocation (CA).

Aim: To assess the impact that the switch from CA of urgent cases to TWG would have with respect to workload, patient throughput, and final diagnosis of the patients referred to the medical GI department.

Method: A record of patient details and their specific allocation were kept after referral letter viewed by GI physician over 3 consecutive months in 2001. One year later, all notes were retrieved and interrogated by a single GI physician recording (a) demographics, (b) presence of TWG symptoms in GP letter, and (c) final diagnosis

Results: 514 notes (out of the 568 referrals) were retrieved. 510 had their first appointment allocated to the GI medical department. The GI physicians who viewed the referral letter (ie CA) allocated 83 as urgent, 237 soon, and 190 routine. The table shows cancers diagnosed and missed by both methods.

Of those who were CA urgent with no TWG symptoms, there were 3 cancers, 3 gastric ulcers, 5 patients with inflammatory bowel disease, 1 decompensated liver disease, and 1 sclerosing cholangitis.

Abstract 457

	Total	Diagnosed cancers	Missed cancers
CA urgent	85	12	5
TWG urgent	236	12	5

Conclusion: Implementation of the TWG in place of CA leads to an almost threefold increase in number of patients classified as urgent with no increase in the pick up rate of cancer. If there were no associated increase in GI practitioners, it would lead to a delay in seeing

Abstract 455

	Oesophageal cancer			Gastric cancer		
Mortality	Before the rule	After the rule	p Value	Before the rule	After the rule	p Value
12 month	70%	65%	0.17	69%	63%	0.17

patients with some cancers and other important non-malignant conditions.

458 SPECIFIC TARGETING OF CCK-2 RECEPTOR ON GASTRIC CANCER CELLS WITH PENTAGASTRIN ANALOGUES

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Background: We have previously demonstrated expression of the CCK2 receptor in hepatopancreaticobilary cancers and uptake of gastrin analogue peptides by CCK2 expressing tumour cell lines.

Aim: To test the ability of five DOTA or DTPA coupled pentagastrin analogues to undergo specific uptake by CCK2+ receptor bearing gastric cancer cells.

Methods: Five pentagastrin analogue peptides coupled to DOTA and DTPA containing 0–3 D-amino acids (denoted by small case letters) for extra stability in serum were studied (see table).

Peptides were labelled with maleimide Alexa Fluor 488 dye (Molecular Probes, USA). Free dye was removed by dialysis. Labelled peptides were exposed to gastric cancer AGS cells transfected with a CCK2 receptor (CCK2+) or control transgene (VC) at 0.8 μg/ml for 6 hours at 37˚C. In a competition assay, cells also received 8 μM gastrin 17. After incubation, cells were fixed and fluorescence intensity was measured using a Cytofluor fluorescence reader. Cells were also examined under a fluorescence microscope to study intracellular localisation of peptide.

Results: Uptake by CCK2+ cells was observed for all five peptides (both DOTA and DTPA coupled); the highest level of fluorescence was obtained with SM1 DOTA. Fluorescence levels in VC cells were 4–19% of those in CCK2+ cells. Co-incubation of labelled peptide with excess gastrin 17 reduced CCK2+ cell fluorescence levels to those of VC cells. Fluorescent microscope analysis revealed labelled peptide to be localised on the plasma membrane and cytoplasm of CCK2+ cells.

Conclusion: This study shows that the gastrin analogue peptides can target CCK2 bearing cells and therefore are of potential for targeted therapy of CCK2 receptor positive tumours.

Abstract 458

SM1	CEAYGWMDF
SM2	CEAYGW(Nle)DF
SM3	cEAYGW(Nle)DF
SM4	ceAYGW(Nle)DF
SM5	ceaYGW(Nle)DF

459 THE DESMOPLASTIC REACTION: TRANSFORMING GROWTH FACTOR β-1 SECRETION AND LOCAL RENIN ANGIOTENSIN SYSTEM IN A CARCINOID CELL LINE

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Background: The renin angiotensin system (RAS) and transforming growth factor beta-1 (TGFβ-1) are responsible for fibroproliferative changes which can potentially be reduced by pharmacological intervention. Angiotensin II (AngII) may increase TGFβ-1 production and cell proliferation via the Angiotensin II type 1-Receptor (AT_1-R). Desmoplasia is a difficult problem especially in carcinoid patients and may contribute to bowel obstruction and mortality. We hypothesised that carcinoid tumours may induce a desmoplastic reaction through TGFβ-1 secretion. We assessed the effect of Losartan, a selective AT_1-R antagonist and Enalaprilat, an ACE inhibitor on their ability to abrogate RAS and hence TGFβ-1 secretion in a human carcinoid cell line (BON).

Methods: BON cells were cultured in serum free media and exposed to Losartan and Enalaprilat (both at 10^{-6}M, 10^{-8}M, and 10^{-10}M) daily for three days. Proliferation and metabolic activity was assessed. Cell culture supernatant was assayed for AngII and TGFβ-1. Fixed cells were immunostained for AT_1-R and AngII.

Results: Untreated BON cells expressed AT_1-R and AngII; AngII and TGFβ-1 were detected in the supernatant. Losartan did not affect Ang II or TGFβ-1 secretion significantly, but decreased proliferation (10^{-6}M, $p<0.05$). When BON were exposed to Enalaprilat, TGFβ-1 excretion increased (10^{-8}M, $p<0.05$) without a dose dependant trend; AngII decreased at 10^{-10}M ($p<0.05$), but increased at 10^{-8}M and 10^{-6}M ($p<0.05$). Enalaprilat 10^{-6}M increased proliferation ($p<0.05$).

Conclusions: BON cells express the AT_1-Receptor, as well as produce and secrete Angiotensin II and TGFβ-1. Proliferation decreased with Losartan, demonstrating activity of the AT_1-R. However, our results suggest the link between RAS and TGFβ-1 is poorly functioning or does not exist in BON cells. The activity of the AT_1-Receptor merits further investigation since autocrine proliferation may be manipulated pharmacologically in this carcinoid cell line.

460 SMALL INTESTINAL CANCERS IN SCOTLAND 1975–99

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Aims: To analyse time trends for incidence and mortality of patients with small bowel cancers in Scotland from 1975–99 and the morphology and sub-site patterns from 1997–99.

Methods: Incidence and mortality data, ICD-9 code 152 for 1975–96 and ICD–10 code C17 for 1997–99 (the latter also providing sub-site information), were obtained from the Scottish Cancer Registry and General Register Office respectively.

Results: Over the 25 year period incidence rates, which have been consistently higher in males, increased (by 84% in males and 55% in females), whereas mortality rates decreased (by 23% in males and 17% in females) but significantly only in males for the former and females for the latter. There were significant increments in the incidence of the two commonest cancers, adenocarcinomas by 79% and malignant carcinoid tumours by 300%. Few cases occurred below the age of 40 and the prevalence peak was between the ages of 80–84.

Conclusion: Small intestinal cancers in Scotland occur mainly in the elderly and have a male predominance. The trend is one of increased incidence and reduced mortality. Adenocarcinomas and malignant carcinoid tumours are the commonest cancers and occur most frequently in the duodenum and ileum respectively.

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	Morphology (n)				
1997–99 Sub-site (n)	A (70)	M (41)	S (11)	N (21)	O (17)
Duodenum (62)	38	4	2	10	8
Jejunum (24)	10	3	2	7	2
Ileum (61)	18	29	6	3	5
Meckel's diverticulum (5)	0	5	0	0	0
Overlapping (8)	4	0	1	1	2

A, adenocarcinoma; M, malignant carcinoid tumour; S, sarcoma; N, non-Hodgkin's lymphoma; O, other primary cancers.

461 NECROSIS IN HEPATOCELLULAR CARCINOMAS OF EXPLANTED LIVERS FOLLOWING LOCO-REGIONAL TREATMENT BEFORE LIVER TRANSPLANTATION: ASSOCIATION WITH TUMOUR RECURRENCE

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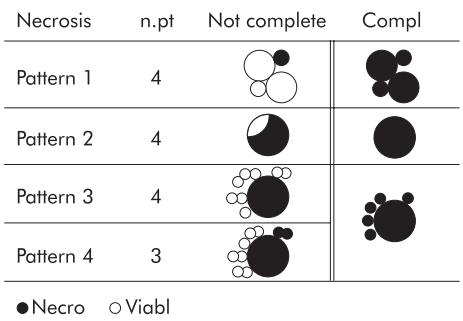
Introduction: All types of local ablation therapy (TACE, TAE, PEI, RFA, MCT, etc) produce necrosis of hepatocellular carcinomas (HCC) but the size and pattern of necrosis and possible prognostic significance for recurrence after liver transplantation (LT) has not been evaluated.

Patients and Method: From 1997 to September 2003, 14 HCC patients, median f.u. 29 m (1–60), M/F 13/1, median age 55, range 46–63) previously treated with TACE (4), epirubicin alone (5), PEI+epirubicin (2), TACE+RFA (1), TACE+TAE (1), TAE (1), (total 25 sessions) underwent LT. Median time between last LAT procedure and LT was 156 days (range 27–447). At explant 8 had multifocal HCC (20 nodules in total, 10–70 mm). In explanted livers, for each HCC nodule the percentage and pattern of necrosis was evaluated.

Results: Four histological patterns of necrosis were found: necrosis was variable: 0–0% in 4 (pattern 1,2,2,3, size 33–70 mm); 10–50% in 3 (all with pattern 1, size 10–40 mm); 75–100% in 7 (pattern 2,2,3, 3,3,4,4, size 15–70 mm). HCC recurred in 3 at 23, 26, and 53 months, all with 10% necrosis or less. The recurrence was not related to the pattern of necrosis or to the time between last LAT procedure and LT.

Conclusion: The amount of LAT induced necrosis in explanted livers may be a good prognostic factor for HCC recurrence. This type of histopathological evaluation can help to identify patients with high risk of recurrence that would need closer follow up, and be eligible for secondary prevention trials after OLT.



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462 HEPATOCELLULAR CARCINOMA TREATED BY ORTHOTOPIC LIVER TRANSPLANTATION: PREDICTION FOR RECURRENCE

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Background: Although liver transplantation (LT) for hepatocellular carcinoma (HCC) can be curative a 25% recurrence by 5 years is limiting.

Aim: Evaluate predictive factors for HCC recurrence after LT.

Patients and Methods: From October 1988 to June 2003, 96 OLT for cirrhosis and HCC were performed. Mean follow up 38.2 m, range (1–120); M/F 81/15, median 55 years (range 31–68), HBV/HCV in 58%. Waiting list time was median 36 days (range 1–370) with no drop outs. Pre OLT locoregional therapy in 42%. Incidental (explant) diagnosis in 23%. Twenty three variables (demographical, tumour characteristics, severity of liver disease, waiting time, and interval between diagnosis to OLT) were assessed by univariate/multivariate analysis.

Results: 15 (15.6%) had HCC recurrence, median 19 months (range 1–58) associated univariately: (1) α FP>200 ng/ml ($p=0.02$), (2) non-incidental diagnosis ($p=0.022$), (3) size of largest nodule at histology ($p=0.01$) independent of the total number of tumour nodules, (4) presence of satellite nodules in explanted liver ($p=0.04$). By multivariate analyses the size of the largest nodule in the explant was the only parameter significantly related to recurrence ($p=0.017$). A cumulative risk (Cox regression) of HCC recurrence and categorised histological size (cut off 25 mm, the median diameter) showed a strong association for nodules >25 mm and recurrence, independently from number of nodules. Microvascular invasion was 42% *v* 17% for>25 mm/<25 mm nodules. No significant association was found between waiting time nor the Milan criteria, and recurrence after OLT.

Conclusions: This consecutive series with a short median waiting time shows that only size of the largest tumour nodule in explants, independent of the total number, had prognostic significance for recurrence after OLT. If the extension of the Milan criteria are justified, this could be >3 nodules <2.5–3 cm. More prospective studies stratified for waiting time intervals are needed to identify good prognostic models of recurrence.

463 TREATMENT WITH THE SELECTIVE COX-2 INHIBITOR ROFECOXIB IS ASSOCIATED WITH INCREASED ENDOTHELIAL CELL APOPTOSIS AND DECREASED VASCULARITY OF HUMAN COLORECTAL CANCER LIVER METASTASES

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Introduction: Treatment with the selective cyclooxygenase (COX)-2 inhibitor rofecoxib (25 mg daily; mean duration 26 days) is associated with a 29% decrease in mean microvessel density (measured by ''hotspot'' counting) in colorectal cancer (CRC) liver metastases compared with tumours from patients treated with placebo only (*Gastroenterology* 2003;**125**:716). These data suggest that rofecoxib may have anti-angiogenic activity against CRC. Coxibs induce apoptosis of endothelial cells (EC) in vitro and in vivo. Therefore, we tested the hypothesis that rofecoxib treatment is associated with increased EC apoptosis in human CRC liver metastases.

Methods: A novel, dual immunohistochemical technique (incorporating anti-CD31 and antisingle stranded DNA antibodies) was used to detect apoptotic EC in metastasis tissue from the phase II clinical trial. Sections were scored using a custom image analysis system (blind to the treatment allocation of each section).

Results: Double +ve (apoptotic) EC grouped together in a subpopulation of vessels in metastases. The total metastasis vessel density (number of CD31 +ve vessels per unit tumour area) was lower in rofecoxib-treated metastases (mean (SEM) 270 (40); n=23) than placebo treated tumours (387 (77); n=19; $p=0.16$). The metastasis EC apoptosis index (AI; the number of double +ve cells per unit EC area) varied widely between individual tumours. The mean ECAI (SEM) was higher in rofecoxib treated metastases (226 (135)) than in metastases from the placebo group (99 (21); $p=0.4$). Similar findings were obtained when ECAI values were calculated as the number of double +ve cells divided by the total metastasis vessel number.

Summary: A novel immunohistochemical technique for detection of apoptotic EC in formalin fixed human tissue has been developed. Rofecoxib may induce apoptosis of EC leading to vessel regression and possible antiangiogenic activity in vivo.

464 USE OF 5-ASA IS ASSOCIATED WITH DECREASED RISK OF DYSPLASIA AND COLON CANCER IN ULCERATIVE COLITIS

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Background: Risk factors for dysplasia and colon cancer (CRC) in UC include: duration and extent of disease, younger age of diagnosis, family history of CRC, and primary sclerosing cholangitis (PSC). Mesalazine (5-ASA) is a mainstay of UC treatment and has been suggested to have chemopreventive properties.

Aim: To determine the effect of 5-ASA use on risk for dysplasia and CRC in chronic UC.

Methods: UC patients with dysplasia or CRC followed at the University of Chicago IBD Centre were matched with controls by disease duration, extent, and age at diagnosis. History of PSC, family history of CRC, and smoking were also reviewed. Chart review was performed by two data abstractors, and a third reviewer resolved discrepancies. Any 5-ASA products used during the duration of disease were converted to mesalazine equivalents. Total amount of 5-ASA over the duration of disease as well as mean daily amount of drug was calculated. Conditional logistic regression was used to examine the relationship of 5-ASA to the risk of dysplasia or CRC. Potential confounding was controlled in a multivariable model.

Results: 26 cases (8 CRC, 18 dysplasia) were matched to 96 controls. Cases and controls were similar in age (mean 46 *v* 48 years), age at diagnosis of UC (mean 33 *v* 34 years), duration of UC (mean 14 *v* 11 years), and extent of disease (17% proctitis, 25% left sided, 58% pancolitis), as well as sex, family history of UC, history of PSC, and history of smoking. Cases were more likely to have a family history of CRC as compared with controls (27% of cases, 9% of controls, $p=0.036$). Conditional logistic regression adjusted for duration of disease, age of diagnosis, and family history of CRC shows that 5-ASA use $\geq$1.2 g/d was associated with 76% reduction in the odds of dysplasia/CRC ($p=0.024$). In addition, as the total dose of 5-ASA increased, the odds of dysplasia or CRC decreased to a statistically significant degree.

Conclusions: 5-ASA $\geq$1.2 g/d in chronic UC is associated with a significant risk reduction of dysplasia and CRC. This supports a chemopreventive role of 5-ASA in the management of chronic UC. (Funded by P&G Pharma).

465 THE EFFECT OF MESALAZINE FOR CHEMOPREVENTION IN EARLY GRADE DYSPLASIA IN ULCERATIVE COLITIS

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Background: Some studies suggest that mesalazine (5-ASA) can attenuate the rate of progression of ulcerative colitis (UC) to colorectal cancer (CRC). Little is known about where in the colitis-dysplasia-carcinoma sequence 5-ASA might function.

Aim: To determine the effect of 5-ASA dose on the progression of UC patients from early grades of dysplasia (defined as indefinite for dysplasia (IND) and flat low grade dysplasia (LGD)) to advanced neoplasia (high grade dysplasia (HGD) or CRC).

Methods: Patients with LGD between 1994 and 2001 were identified by review of our institution's GI Pathology database. Patients with IND were identified by reviewing the records of all UC patients who underwent a surveillance exam in 1996–7 at our institution. The records of all patients were reviewed for 5-ASA dose (adjusted for medication type), other clinical variables, and surveillance history. Progression from time-zero (t_0: discovery of IND or LGD) to advanced neoplasia was the primary outcome measure. Using life table methods and Cox modeling, the effect of low dose 5-ASA (average daily dose$<$1.6 g/d) was compared with high dose 5-ASA ($\geq$1.6 g/d) either at, or following, t_0.

Results: We identified 69 patients with early grade dysplasia: 23 LGD, 46 IND. Average duration was 21 years; 90% had extensive colitis; and average age was 50 years. All but 7 were taking 5-ASA at t_0. 14 (17%) progressed to advanced neoplasia. In the IND stratum, no patients (0/28) on high dose 5-ASA progressed, whereas 4 of 28 on low dose 5-ASA did. By life tables this difference carried a p value of 0.09. Exclusion of SSZ users (who are seldom prescribed high doses) did not alter the results. Disease duration, disease extent, and age at t_0 were not predictive of progression on univariate or multivariable testing.

Conclusions: High dose 5-ASA at the time of detection of IND or LGD appears to protect against progression to advanced neoplasia. As subsequent dose appears to be a less important predictor of progression, the effect of 5-ASA is likely to occur early in the colitis-dysplasia-carcinoma sequence. Further studies investigating the effect of 5-ASA in preventing IND or LGD should be considered.

466 PREVALENCE AND CHARACTERISTICS OF FLAT AND DEPRESSED COLORECTAL NEOPLASMS IN A WESTERN POPULATION: A PROSPECTIVE STUDY BY A JAPANESE TRAINED ENDOSCOPIST

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Background: Flat and depressed colorectal neoplasms have been widely investigated in Japan and recently in Western countries with incidence rate of 6.8%–48.5%. This wide variation reflects differences in population characteristics or colonoscopic technique. The aim of this study was to determine the prevalence of flat neoplasms in the UK by a colonoscopist trained in Japan.

Methods: A prospective analysis of 1000 consecutive colonoscopies was performed. Macroscopically the lesions were classified according to the classification described by Japanese Society for Cancer of the Colon and Rectum and histological diagnosis was made based on WHO system.

Result: Total colonoscopy (adjusted) was achieved in 98% of patients. Indications for colonoscopy were: neoplasia surveillance (211), change in bowel habit (179), bleeding (160), assessment of IBD (141), family history of colorectal neoplasms (106), anaemia (86), and others (117). In total 1075 polyps were found in 412 patients, which include 25 cases of advanced cancer. 758 polyps were histologically proven to be neoplastic. Of these, 617 were classified as polypoid (81%) and 141 flat (IIa, IIb, IIc) (19%). A higher incidence of advanced pathology (severe dysplasia or Dukes'A adenocarcinoma) was observed in flat and depressed neoplasms (0% in IIa, 14% in IIb, IIc) than in polypoid ones (2%).

Conclusion: A Japanese trained endoscopist found flat neoplasms represented 19% of all adenomas (flat/depressed 0.3%), which is lower than previously reported incidence.[1] Flat elevated (IIa) and polypoid lesions appeared to have similar characteristics, while flat (IIb) or depressed lesions (IIc) contain more advanced pathology. Flat and depressed neoplasms are rare finding but exist in a Western population.

1. Rembacken BJ. *Lancet* 2000 (355).

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	Mild/mod	Severe/Ca	Neoplastic/polyp
Polypoid (Is, Isp, Ip)	606 (98%)	11 (2%)	69%
Flat elevated (IIa)	119 (100%)	0 (0%)	89.5%
Flat & depressed (IIb, IIc)	19 (86%)	3 (14%)	100%

467 DENDRITIC CELLS FROM PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS AND COLORECTAL CANCER DISPLAY AN IMMATURE PHENOTYPE—A MECHANISM OF IMMUNE DYSREGULATION PERMISSIVE TO CANCER DEVELOPMENT

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Introduction: Dendritic cells (DCs) are professional antigen presenting cells with a critical role in antitumour immune responses. Alterations in the surface phenotype of peripheral blood DCs, including reduced expression of co-stimulatory molecules (CD80 and 86) necessary for effective T cell activation have been observed in patients with haematological malignancies.[1,2] To our knowledge this is the first study aimed at investigating the maturation status of circulating DC populations in individuals affected by the pre-malignant condition FAP.

Methods: Using a whole blood assay and multicolour flow cytometry, DCs were identified in the peripheral blood of FAP and CRC patients as an HLA DR+Lineage–(CD3, CD14, CD16, CD19, CD34, CD56) population. The absolute number of circulating DCs per microlitre of whole blood, and the surface expression of the co-stimulatory molecules CD80 and CD86, were calculated using the Super-enhanced normalised Subtraction facility of the Win List programme.

Results: The absolute number of Lineage -HLA DR+putative DCs per microlitre of blood was not significantly different in CRC, or FAP patients as compared to controls. Interestingly there was a significant reduction ($p<0.009$) in the number of CD86 positive cells ($p<0.009$) in both patient groups, and of CD80 positive ($p<0.05$) cells in the CRC patients. (FAP n=16, CRC n=12).

Conclusion: The total number of circulating DCs is preserved in FAP patients and individuals with colorectal carcinoma. However, these cells have an immature phenotype with reduced numbers of cells expressing co-stimulatory molecules, and this may be an important mechanism of tumour escape from immunological control.

1. Eisendel BJH. 2003;**120**:63–73.
2. *Orsini Cancer Research* 2003;**63**:4497–506.

468 PEANUT LECTIN CAUSES COLONIC PROLIFERATION VIA INTERACTION WITH CD44V6 AND SUBSEQUENT C-MET AND MAP KINASE PHOSPHORYLATION—A POSSIBLE MECHANISM FOR BACTERIA INDUCED COLONIC PROLIFERATION

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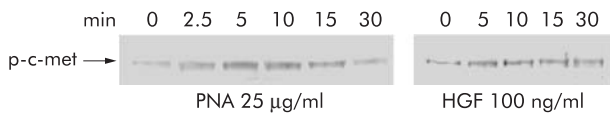
CD44 splice variants and the receptor tyrosine kinase c-Met have independently been identified as tumour metastasis associated proteins and are predictors of tumour invasion and poor prognosis in colon cancer. The presence of CD44v6 splice variants correlates with colonic crypt proliferation (*Histopathology* 1998;**32**:317–21) and has recently been shown to be essential for c-Met activation by its ligand HGF/SF (*Genes Dev* 2002;**16**:3074–86). We earlier reported that CD44 splice variants are the major cell surface binding proteins for the pro-proliferative galactose binding dietary peanut lectin/agglutinin (PNA) (*Glycobiology* 2001;**11**:587–92). Here we show by co-immunoprecipitation that CD44v6 and c-Met physically associate with each other in HT29 colon cancer cells, and that PNA induces phosphorylation of c-Met and subsequently MAP kinase.



Abstract 468 Phosphorylation of c-Met in response to PNA and HGF/SF.

We also report that the expression of CD44 splice variants and c-Met depends upon growth and differentiation status of colon cancer cells. In HT29 cells, overall CD44 expression increases after confluence whereas CD44v6 and c-Met are both strongly expressed in actively growing pre-confluent cells but decline dramatically post-confluence, in response to 1 mM butyrate and also to the MAPK kinase inhibitor UO126.

Differential expression of CD44 splice variants suggests that they have distinct roles. This splice variation is known to be regulated by proinflammatory cytokines such as IL-8. The interaction between the pro-proliferative dietary PNA lectin and CD44v6 which results in subsequent c-Met and MAPkinase phosphorylation could be a model for proliferative effects of bacterial lectins on the colonic epithelium.

469 METHYLATION STUDIES IN COLONIC POLYPS AND CANCERS

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Background: It is well established that alterations in patterns of DNA methylation play an important role in the progression of colorectal cancers. Less is known of the relevance of this process to the development of colonic polyps. It is however likely that patterns of genetic change influence the phenotype of a polyp and its subsequent risk of progression to cancer.

Aims: The aims of this study are to ascertain the role of methylation in colonic polyps; and to determine the clinicopathological correlates of methylation abnormalities in colonic precursor lesions.

Methods: DNA methylation changes were assessed in fresh representative samples of adenomas, hyperplastic polyps, colorectal cancers, and normal mucosa. Global methylation levels were measured by analyzing the DNA methyl accepting capacity. Methylation of p16, hMLH1, and MINT 1, 2, 12, and 31 were assessed by bisulfite polymerase chain reaction. Microsatellite status was determined by polymerase chain reaction using six markers, and hMLH1 and proliferating cell nuclear antigen expression was assessed by immunohistochemistry.

Results: Methylation studies showed that normal colonic mucosa had a higher endogenous 5-methyl cytosine content than all proliferative lesions of the colon ($p<0.001$). The extent of demethylation in hyperplastic polyps and adenomas was significantly related to its proliferative rate. Right sided hyperplastic polyps were more likely to be methylated than adenomas (odds ratio, 2.3; confidence interval, 1.1 to 4.6). There was no relation between the level of global hypomethylation and hypermethylation. Some hyperplastic colorectal polyps have the propensity to develop dense CpG island methylation.

Conclusions: Hypermethylation and hypomethylation contribute separately to the process of carcinogenesis. It is likely that a proportion of hyperplastic polyps can progress to colorectal cancer.

470 PREDICTIVE VALUE OF VEGF-C EXPRESSION AND TUMOUR SPROUTING FOR NODAL INVOLVEMENT IN SUBMUCOSAL INVASIVE COLORECTAL CARCINOMAS

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Aim: It is difficult to estimate the adequacy of endoscopic resection for submucosal invasive colorectal carcinoma (SICC) because about 10% of patients with SICCs have nodal involvement. VEGF-C is suggested to have an important role for tumour lymphangiogenesis and tumour sprouting has regained attention as an indicator of lymphatic invasion (LI). To investigate risk factors of nodal involvement in SICC, we have examined the relationship between nodal involvement and tumour status of VEGF expression and tumour sprouting along with clinicopathological factors.

Methods: 107 consecutive patients with SICCs underwent either surgical or endoscopic resection between 1990 and 2001. Patients were aged between 38 and 83 years (median 64), 70 were male. 36 tumours were polypoid. Tumours were classified by the absolute amount of submucosal invasion both in their depth and width (depth; $sm1 \leqslant 0.5$ mm, $0.5<sm2<1.0$ mm, $1.0 \text{ mm} \leqslant sm3$, width; $sma \leqslant 1.0$ mm, $1.0<smb<3.0$ mm, $3.0 \text{ mm} \leqslant smc$) and were immunohistochemically stained for VEGF-C and Cytokeratin 8/18.

Results: Of 107 tumours 12 had nodal involvement. Among clinocopathologocal factors, the ratio of nodal involvement of polypoid tumours (2/45) was lower than that of non-polypoid (10/62; $p=0.053$). Tumours were divided into sm1 (24), sm2 (43), sm3 (40) in the depth, sma (27), smb (40), smc (40) in the width. There was no nodal involvement in sm1 and sm2a (9). As tumour invasion increased in depth and width, positive cases of LI, venous invasion (VI) and nodal involvement increased. VEGF-C expression and tumour sprouting showed positive correlation with LI and nodal involvement. For nodal involvement, VEGF-C expression showed high specificity (82.0%), tumour sprouting showed high sensitivity (91.7%), respectively.

Conclusion: Combination of VEGF-C expression and tumour sprouting are useful in predicting nodal involvement in SICC.

471 DIETARY INTERACTIONS AND INCEPTION OF COLONIC TUMOURIGENESIS

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Background: Globalisation of Western diet or lifestyle will produce 50% increase in cancer incidence over the next 20 years. Western diet contains mutagenic N-nitroso compounds (NOC) from red meat and diverse pro-oxidant non-mutagenic agents (PONMA). This study tests the hypothesis that model NOCs and PONMA have interactive effects upon key events of colonic tumourigenesis.

Methods: Lambda carrageenan (λCgN) and n-methyl-N-nitrosurea (MNU) were used as model dietary PONMA and NOC, respectively. Study endpoints included DNA adduct formation, crypt stem cell mutations, and mutant clonal expansion in Balb/c mouse colon. A single dose of MNU 62.5 mg/kg was combined with single or recurrent short term or long term λCgN (1% or 4%) exposures, over 10 weeks. Stem cell mutations and mutant clonal expansion were assessed by the metallothionein endogenous reporter gene assay. Assessments were blinded to treatment category. Statistical analysis was by ANOVA.

Results: λCgN treatment did not enhance MNU induced DNA adduct formation. However, all patterns of λCgN intake significantly increased MNU induced stem cell mutations (mean values 30–55 mutations/10^4 crypts) in excess of MNU alone (18 mutations/10^4 crypts) ($p<0.001$). Treatment by λCgN also promoted clonal expansion of mutant crypt stem cells ($p<0.001$) thus increasing total stem cell mutation load for combined λCgN/MNU regimens *v* MNU alone ($p<0.001$).

Conclusions: Model chemicals, representing genotoxic and non-genotoxic components of Western diet, have adverse interactive effects upon stem cell mutations in mouse colon. λCgN increases the sensitivity of colonic mucosa to MNU induced stem cell mutations.

472 TIMING OF OPERATION AFTER RADIOTHERAPY FOR RECTAL CANCER (II)

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Aim: We have reported that following standard radiotherapy radiation induced apoptosis may be a time limited and volume dependent phenomenon and radiosensitive tumours should be surgically resected earlier than the more resistant ones (BSG 2002). We have now examined the relationship between the effect of radiation and expression of apoptosis regulating proteins.

Methods: Patients received standard radiotherapy (40Gy, duration of 4–8 weeks, n = 25). Expression of P53, survivin, apoptotic index (AI), and proliferative index (PI) were immunohistochemically estimated in paired sections of biopsies and post-irradiated resected tumours. The reduction ratio was histologically estimated and radiosensitivity was judged in cases in which over two thirds of tumour tissue was destroyed.

Results: Radiosensitivity ratio and median reduction ratio were 43.5% and 45%. Both the AI and PI of the radiosensitive subgroup (n = 10) were lower than those of the resistant one (n = 15, 2.4 *v* 4.2; $p=0.005$, 25.9 *v* 46; $p=0.005$, respectively). All the radiosensitive tumours had negative or low expression of survivin. Combination of survivin and p53 revealed a subgroup survivin(-)/p53(L) with the highest AI (6.05) and PI (58.7) of all subgroups among the radioresistant tumours. In this subgroup the AI of the surgical specimens exhibited threefold elevation compared with biopsies but there was no difference in the PI level.

Conclusions: Among radioresistant tumours a comnibination of survivin(-)/p53(L) may be linked with greater tumour regression by apoptosis. Identification of these tumours' characteristics may lead to discovering their optimal treatment.

Pancreas posters 473–474

473 MORE SPIN: MAGIC ANGLE SPINNING PROTON NMR STUDIES OF BIOPSY SIZE PANCREATIC SAMPLES

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Introduction: Although there is some consensus with regard to the overall sequence of events in pancreatitis, details of the early stages are still lacking. Consequently diagnosis is often late, and therapeutic measures non-specific and fail to limit disease progression. Despite improvements in supportive and intensive care services some 10% of attacks are fatal and many patients still require protracted, costly stays in hospital and mortality remains high (20%).

Aims: Earlier studies of the pancreas have tended to focus on its endocrine function. Ultimately, however, we want to study metabolism in the human pancreas and particularly that in pancreatitis. Magic Angle Spinning Proton Nuclear Magnetic Resonance (MAS ^{1}H NMR) spectroscopy has previously been used to study directly metabolism in intact samples of liver, brain, and kidney tissue. We now describe the first application of this technique to pancreatic tissue. Our first task was to show that MAS ^{1}H NMR was applicable to pancreatic studies. We here describe the use of ^{1}H NMR spectroscopy to produce a biochemical metabolite profile of pancreata from female mice.

Methods: 400 MHz ^{1}H MAS NMR spectra of small samples of intact tissue (~10 mg) obtained from female mice pancreata were obtained at 3°C using various 1D and 2D pulse sequences. The ^{1}H NMR spectroscopic profile, which was robust and stable over the experimental period (15 h), was dominated by signals from a range of amino and organic acids, together with resonances deriving from lipoproteins and choline molecules.

Conclusions: This work shows that MAS H^1 NMR is applicable to biopsy size samples, the results are compatible with that of the classical amino acid consumption test and provide a window for the direct study of metabolism in a hitherto largely inaccessible organ to finally be elucidated.

474 USING MACHINE LEARNING TO PREDICT SEVERITY IN ACUTE PANCREATITIS

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Background: Acute pancreatitis (AP) has a very variable course. Accurate early prediction of severity is useful to direct clinical care and to stratify patients for trials. Current assessment tools are inaccurate and unable to adapt to new parameters. None of the current systems uses C-reactive protein (CRP). These problems can be overcome using modern machine learning tools.

Methods: The admission data were evaluated from case notes of 370 patients admitted with AP to QAH between 1996 and 2001; after exclusions 265 patients with complete data were studied. Physical examination and full blood count, Vicker's profile, CRP, and arterial blood gases were recorded. Aetiology, severity, and complications were also recorded. A logistic regression model was used to identify the relation between the input features and the outcome of patients in the sample. Bootstrapping, a machine learning technique, was used to make the best use of data and obtain confidence estimates on the parameters of the model. Redundant features were removed from the model using feature selection based on these confidence estimates.

Results: A linear model containing 8 variables (age, CRP, respiratory rate, pO2 on air, arterial pH, serum creatinine, white cell count, and GCS) predicted a severe attack with an area under the receiver-operating characteristic curve (AUC) of 0.81 (standard deviation 0.01). This was significantly better than admission-APACHE II in the same patients (AUC 0.74) and historical admission-APACHE II data (AUC 0.68 to 0.75). The optimum cut off value for predicting severity gave a sensitivity and specificity of 0.87 and 0.71 respectively.

Comments: This system for the first time combines scoring of systemic disturbance and admission CRP value for the prediction of severe AP. The score is simple to use, and more accurate than admission APACHE-II. It is adaptable and would allow easy incorporation of new predictive factors such as CAPAP and IL6.

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475 AN UNUSUAL CASE OF SPONTANEOUS DISINTEGRATION OF A LARGE OESOPHAGEAL POLYP WITH A LONG STALK

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Case report: An 80 year old man was admitted with haematemesis in March 2001. Clinical examination was normal. In 1998 he had experienced the presence of a large lump in his throat during an episode of vomiting. As he could not vomit it out, he put his fingers in the mouth to push it back into the gullet. He was not investigated at that time. At endoscopy a pedunculated oesophageal polyp of 4 cm diameter hanging down at the oesophagogastric junction (OGJ) with an 18 cm stalk originating in the subcricoid region was seen. The surface of the polyp was ulcerated but there were no stigmata of recent haemorrhage. The histology was not helpful. Barium swallow showed hypotonic oesophagus but the mass could not be seen. Computerised tomography with intravenous and oral contrast showed dilatation of the oesophagus with a soft tissue mass at the OGJ with a stalk arising from subcricoid region. There was no evidence of lymphadenopathy or distant metastasis. Magnetic resonance angiogram did not show any major blood vessel in the stalk. However this lesion had disappeared in February 2002 when endoscopy was done for removal of this polyp. It was felt that the polyp might have been lost as a result of ischaemic necrosis, possibly following torsion or by outgrowing its blood supply. Further repeat endoscopy in May 2003 did not reveal any mucosal abnormalities. This polyp clinically behaved like a fibrovasular polyp but histological proof could not be obtained.

Discussion: Fibrovascular polyps are characterised by the development of pedunculated intraluminal masses that can reach gigantic size and may have spectacular clinical presentations. Most common clinical symptom is oral regurgitation of fleshy mass, and dysphagia and weight loss are also common. Diagnosis by barium swallow and endoscopy may be difficult and resection of these lesions is necessary. Small polyps may be resected endoscopically. Where this is not possible surgical resection may be necessary. Often oesophagotomy with lateral cervical approach is necessary. To our knowledge, spontaneous resolution of this problem has not been reported so far.

476 INTRACTABLE NAUSEA VOMITING AND PAIN: ''FUNCTIONAL'' OR PHYSIOLOGICAL

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Introduction: We report the case of a patient who shows the importance of gastric function testing in functional dyspepsia.

Case history: KB is a 22 year old white female with a five year history of abdominal symptoms. In August 1998, while on vacation, she contracted campylobacter which caused severe nausea, vomiting, cramps, and diarrhoea. Her mother and sister contracted the same illness and recovered quickly whilst KB continued to suffer with upper abdominal pain, nausea, and vomiting. By February 1999 she had lost 3 stone in weight. She was referred for investigation and underwent repeated upper endoscopy, colonoscopy, small bowel follow through (SBFT), and abdominal ultrasound. All tests were reported normal except for SBFT which suggested an area of Crohn's, beyond the range of the endoscope. She then underwent a laparotomy which was reported entirely normal.

KB continued to vomit and was referred to a tertiary centre where irritable bowel syndrome was diagnosed. Despite her conviction that the symptoms were organic, she was referred psychological counselling. This failed to implicate a bulimic disorder and symptoms persisted. In 2000, KB was referred to the Royal Free for a further opinion. Gastric emptying study revealed profound gastroparesis, abnormal gastric slow wave activity, and gallstones. In July 2001 she underwent a laparoscopic cholecystectomy which failed to improve her symptoms. Gastric pump failure was treated with a range of prokinetic agents without effect and two pyloric botulinum injections failed to relieve the nuasea, pain, and vomiting. At this point, an Enterra neurostimulator was inserted but following a brief period of improvement, the symptoms recurred. This treatment was followed by the surgical insertion of a percutaneous jejunostomy tube and a gastrojejunostomy. This gastric bypass has stopped the daily vomiting and improved her pain. The nausea persists but is relieved by antiemetics.

Conclusion: This case clearly illustrates the need to exclude gastroparesis in patients with ''functional'' dyspepsia. Treatment is complex and may require neurostimulation or gastric bypass.

477 A CASE OF OBSCURE GASTROINTESTINAL BLEEDING

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Introduction: Up to 5% patients with gastrointestinal (GI) bleeds have normal initial investigations (endoscopy and colonoscopy) and a definitive diagnosis can be a challenge. In such cases it is necessary to proceed to further investigations. However it can be difficult to decide on the most appropriate test in different clinical situations, especially as the options available will vary between hospitals.

Case report: RK is a 32 year old respiratory registrar who collapsed while conducting an outpatient clinic. He was found by his consultant surrounded by fresh melaena and, following resuscitation, underwent an endoscopy. This was normal, as was a subsequent colonoscopy with terminal ileal intubation. He had one further significant bleed during his inpatient stay and required a total of 6 units of blood.

While in hospital, he also underwent 2 mesenteric angiograms (one immediately after his second bleed where he became haemodynamically unstable), a labelled colloid scan and a labelled red blood cell scan. These were all normal.

As an outpatient he went on to have a small bowel meal, an enteroscopy which visualised small bowel 70 cm distal to the pylorus, an abdominal computerised tomography scan, a Meckel's scan, capsule endoscopy, and finally a laparoscopic assisted enteroscopy.

Conclusions: This case report discusses the options that are available when investigating GI bleeds of obscure origin and explains the rationale for each procedure. In particular, it discusses the benefits of the individual investigations, so that informed decisions can be made about the most appropriate test in each situation.

The management of this case involved gastroenterologists, radiologists, and general surgeons and highlights the multidisciplinary approach that is needed to make a definitive diagnosis in cases of obscure GI bleeds.

478 IRON DEFICIENCY ANAEMIA IN THE ELDERLY

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Case report: An asymptomatic, frail 92 year old woman was found to have a normocytic anaemia. A gastroscopy showed a large hiatus hernia and mild antral gastritis. Duodenal biopsies were normal. Subsequently the haematinics were checked and she was found to have a low ferritin.

Six months later she presented with a history of two months true diarrhoea and 10 kg loss of weight. There was no rectal bleeding. Examination, abdominal radiography, and stool cultures were normal. Nonetheless she was found to still be anaemic. In addition her C-RP was mildly raised and her albumin and serum potassium low. It was felt certain that she had developed a colonic neoplasm.

However, surprisingly a flexible sigmoidoscopy revealed moderately active ulcerative colitis to at least the splenic flexure. This was successfully treated with Asacol, Predfoam, and prednisolone.

Discussion: This descriptive report raises several important points to consider when managing elderly patients with iron deficiency anaemia. Firstly, it highlights that it is important to measure the haematinics as soon as a patient is found to be anaemic. Secondly, it raises the question as to whether iron deficiency alone would merit investigation in the same way as iron deficiency anaemia. Thirdly, it emphasises that it is important to investigate both upper and lower gastrointestinal tracts in patients diagnosed with iron deficiency anaemia, and raises the question as to whether this is really necessary if a lesion is found at the initial investigation. Fourthly, this case shows that inflammatory bowel disease can present de novo in the extreme elderly and therefore provides a reminder that it should always be included in the differential diagnosis of chronic diarrhoea. Finally, until now the oldest age of presentation of ulcerative colitis reported in the literature was 85 years; with the publication of this case report it is now 92 years.

Conclusion: Evidence based answers to the above questions will be provided in the interactive case report, although there are no data to determine whether the proximal colon of this patient should now be investigated.

479 ACUTE CHOLESTATIC HEPATITIS ASSOCIATED WITH ATORVOSTATIN

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Introduction: Hydroxymethylglutaryl coenzyme-A (HMG Co-A) reductase inhibitors (or statins) are well recognised as a cause of mild and usually transient hepatitis. Cholestatic liver injury however, has been reported in only 3 patients in association with atorvostatin. We report a further 2 cases.

Case reports: A 57 year old woman with a history of hypertension and hypercholesterolaemia was commenced on atorvostatin 10 mg daily. There was no history of excess alcohol consumption. Four weeks later she presented with jaundice and dark urine. Clinical examination was normal. A biochemical work-up showed an increased bilirubin concentration of 584 umol/l, aspartate aminotransferase (AST) 596 IU/l, alanine aminotransferase (ALT) 931 IU/l, alkaline phosphatase 156 IU/l and Υ-glutamyl transferase (Υ-GT) 247 IU/l. The results of a serological test for viral hepatitis, iron studies, antimitochondrial, antinuclear, and antismooth muscle antibodies were negative or normal. A liver biopsy showed an acute cholestatic hepatitis. The atorvostatin was withdrawn and the liver function tests improved markedly. On review2 months later the only abnormality was a Υ-GT of 99 IU/l.

A 63 year old man presented for investigation of abnormal liver function test results. He had started taking atorvostatin in the 3 months preceding his referral, liver function tests at the time being normal. He consumed 30 units of alcohol per week. Repeat blood tests showed a bilirubin of 18.4 umol/l, AST 241 IU/l, ALT 283 IU/l, alkaline phosphatase 216 IU/l, and Υ-GT 153 IU/l. A full liver screen and abdominal ultrasound were normal. A liver biopsy showed a chronic hepatic process. The liver function normalised within 8 weeks of cessation of treatment.

Conclusion: Clinicians should be aware of the ability of atorvostatin and other statins to cause a cholestatic hepatitis with favourable clinical outcome after drug withdrawal.