had stigmata of bleeding at initial endoscopy (adherent clot, visible vessel or active bleeding). 56 (78%) patients had EH (75% Adrenaline, 25% Adrenaline plus other). 20/56 patients had active bleeding at endoscopy compared with 0/16 in the group that did not receive EH. The re-bleeding rate in the group which had EH was 36% (11/42 Adrenaline only, 9/14 Adrenaline plus other), compared with 31% if no EH was attempted. Of the EH group that re-bled, 10 patients had a further attempt at EH (4 later required surgery), 8 patients went immediately for surgery and 2 died within 24 hours. Amongst those that rebelled without prior EH, 2 had EH (1 required surgery later), 2 had surgery immediately and 1 died early. In total, 15/72 (21%) patients with stigmata of peptic ulcer bleeding required surgery. The mortality rate (<30 days) in patients with stigmata of recent bleeding was 16%, while overall mortality for all bleeding peptic ulcer patients was 14%.

Conclusion: Only 78% of patients with stigmata of bleeding peptic ulcer had EH at initial endoscopy. The re-bleeding rate following EH was higher than available RCT data. Endoscopic management (such as repeat EH for re-bleeding) performed in experienced centres in the setting of a RCT requires validation in individual endoscopy units.

Plenary Posters: 048-081

048 A NOVEL METHOD FOR STUDYING THE CORTICAL PROCESSING OF HUMAN SWALLOWING USING SYNTHETIC APERTURE MAGNETOMETRY (SAM)

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Background/Aims: Positron emission tomography has been applied to study cortical activation during human swallowing, but employs radio-isotopes precluding repeated experiments and has to be performed supine, making the task of swallowing difficult. Here we now describe Synthetic Aperture Magnetometry (SAM) as a novel method of localising and imaging the brain's neuronal activity from magnetoencephalographic (MEG) signals to study the cortical processing of human volitional swallowing in the more physiological prone position.

Methods: In 3 healthy male volunteers (age 28-36), 151-channel whole cortex MEG (Omega-151, CTF Systems Inc.) was recorded whilst seated during the conditions of repeated volitional wet swallowing (5mls boluses at 0.2Hz) or rest. SAM analysis was then performed using varying spatial filters (5-60Hz) before co-registration with individual MRI brain images. Activation areas were then identified using standard stereotactic space neuro-anatomical maps. In one subject repeat studies were performed to confirm the initial study findings.

Results: In all subjects, cortical activation maps for swallowing could be generated using SAM, the strongest activations being seen with 10-20Hz filter settings. The main cortical activations associated with swallowing were in: sensorimotor cortex (BA 3,4), insular cortex and lateral premotor cortex (BA 6,8). Of relevance, each cortical region displayed consistent inter-hemispheric asymmetry, to one or other hemisphere, this being different for each region and for each subject. Intra-subject comparisons of activation localisation and asymmetry showed impressive reproducibility.

Conclusion: SAM analysis using MEG is an accurate, repeatable, and reproducible method for studying the brain processing of human swallowing in a more physiological manner and provides novel opportunities for future studies of the brain-gut axis in health and disease.

049 GASTRIC ACID IN THE CARDIA ESCAPES BUFFERING BY FOOD AND REMAINS HIGHLY ACIDIC AFTER MEALS

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Background: Gastroesophageal reflux typically occurs after meals. Previously we have shown that this postprandial refluxate is often more acidic than the contents of the body of the stomach after a meal. This suggested variation in intragastric pH after a meal, with an area of high acidity in the proximal stomach remaining unbuffered by food.

Aims and methods: This study aimed to directly measure the pH profile of the proximal stomach. Ten healthy subjects underwent dual pH electrode pull through studies under fasting and then postprandial conditions. The pH catheter was positioned in the stomach and then withdrawn by 1cm increments. The pH at each catheter position and the distance of the step-up to oesophageal pH was measured in each subject.

Results: Under fasting conditions the pull through studies revealed a stable intragastric pH throughout the stomach, median pH 1.5 (range 0.7-1.9). When the pull through studies were repeated after a meal the extent of food related buffering varied throughout the stomach. Postprandially the cardia remained highly acidic compared to the body of the stomach, median pH 1.4 (range 0.9-5.0) vs median pH 4.6 (range 2.0-6.7) ($p < 0.01$). After the meal the pH step-up from gastric to oesophageal pH was noted to be a median of 2cm (range 1-3cm) more proximal than under fasting conditions ($p < 0.05$).

Conclusions: The cardia region of the stomach experiences meal stimulated acid secretion but escapes the buffering effect of meals. After a meal an area of high acidity (equivalent to fasting pH) was recorded at electrode positions just below the pH step-up point. The presence of this unbuffered pocket of acid immediately below the gastro-oesophageal junction is likely to be an important factor in the pathogenesis of gastro-oesophageal reflux disease.

050 PATTERNS OF PRESCRIBING LONG-TERM H₂ RECEPTOR ANTAGONISTS IN PRIMARY CARE: ROLE OF HELICOBACTER PYLORI INFECTION. A CROSS SECTIONAL SURVEY

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Background: Dyspepsia is a common problem in the community requiring patients to be maintained on long-term acid suppression. Nonetheless the prevalence of *Helicobacter pylori* in this subgroup of patients has never been assessed before.

Aim: This cross sectional survey was designed to assess the indications/costs for prescribing long-term H₂ receptor antagonists (H₂RA) in general practice with particular reference to *Helicobacter pylori* (HP) infection.

Patients and methods: Six large primary care groups (PCG), in the Humber area were studied. Patients who met the entry criteria were invited for an interview and serological determination of their HP status.

Results: 1034 (1.5%) patients were on long term H₂RA. Peptic ulcer disease (PUD) was the commonest indication for prescribing (35%) followed by Non ulcer dyspepsia (NUD), 22% and Gastro-oesophageal reflux disease (GORD), 18%. In 82% of the patients treatment with H₂RA therapy followed a previous endoscopic or radiological investigation. Only 27 (2.5%) patients had had their HP status checked within the last 6 months. Of the 471 patients who eventually had their HP serology tested, 271 (63%) were HP positive. Fifty eight percent of the HP positive patients had PUD while the majority of HP negative patients had either GORD (32%) or NUD (29%). The duration of therapy was significantly longer in the HP positive patients (8.3 ± 0.3 vs 6 ± 0.8 , $p < 0.00001$), especially those with PUD. The mean symptom score was also significantly higher in the positive patients (7.1 ± 0.2 vs 6 ± 0.2 , $p < 0.0008$).

Conclusion: A significant proportion of patients in primary care are on long term H₂RA, imposing a considerable financial drain on the NHS resources. Approximately two thirds of these patients will be HP positive, and amongst them the largest group will comprise of patients with PUD. Since these are the patients most likely to benefit from HP eradication, stringent attempts should be made to identify them.

051 NON-INVASIVE HP TESTING VERSUS ENDOSCOPY WITH HP TESTING FOR DYSPESIA

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Introduction: There is interest in using non-invasive *H. pylori* (H.P.) testing in place of endoscopy for investigating dyspepsia.

Aim: To compare by prospective randomised trial HP breath test versus endoscopy plus *H. pylori* testing in dyspepsia.

Patients and methods: The study involved 708 consecutive patients (mean age = 36 years, range 17-57) (53% males) referred for investigation of upper GI symptoms. Patients with sinister symptoms

or taking NSAIDs were excluded. Epigastric pain/discomfort was the predominant symptom in 53% and heartburn/reflux in 29%. The patients were randomised in double blind fashion to ^{14}C -urea breath test (BT) or endoscopy with *HP* testing (E). All *HP* positives were given triple therapy and the negatives treated according to symptoms $\pm$ endoscopy findings. Outcome was assessed by an independent investigator at 1 year.

Abstract 51, Table 1

Outcome at one year	Breath test	Endoscopy (n=352)
Mean Glasgow Dyspepsia Score	5.6	5.4
% attending GP since randomised	37%	33%
% attending hospital since randomised	6.2%	6.2%
Patients' concern about missed pathology	104	1.5
Patients' satisfaction with management	5.3	5.3

Results: One year follow-up was 83%. *HP* prevalence was 48% in the BT group and 51% in the E group and eradication rates at one year 84% and 79% respectively.

The above scores remained similar when patients subanalysed according to predominant symptom or *HP* status on presentation. Of the 356 patients randomised to BT, only 24 (6.7%) were referred for subsequent endoscopy showing no abnormality in 17, mild oesophagitis in 5, DU in 1 and failed examination in 1. Of the 352 patients randomised to endoscopy, no pathology was identified which required treatment other than *HP* eradication or symptomatic management.

Conclusion: This large, randomised prospective study indicates that BT is as effective and as safe as endoscopy in this patient population and should be the investigation of choice on account of its lower cost and less invasive nature.

052 GASTRIC SECRETION OF AMOXICILLIN AND METRONIDAZOLE IS INCREASED BY PRONASE, A LUMINAL MUCOLYTIC

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Introduction: Reduced gastric mucus thickness has been associated with enhanced *Helicobacter pylori* eradication rates. Furthermore the addition of the mucolytics pronase and N-acetyl cysteine to antibiotic regimens has also been shown to be beneficial.

Aim: To use a rat model to investigate the impact of pronase on mucus thickness and gastric antibiotic secretion.

Methods: Fasted male rats were anaesthetised. At laparotomy a cannula was inserted via a duodenal incision into the gastric lumen, which was washed and then filled with 1.5 mL of 0.9% saline or 20 mg/mL pronase solution. Gastric acid secretion was inhibited by i.v. omeprazole. After a 30-minute run-in, either metronidazole, amoxicillin or clarithromycin was infused intravenously. Every 15 minutes for 2 hours, plasma was sampled and gastric luminal contents were aspirated and replaced with fresh solution. Samples were analysed by narrow-bore HPLC. Gastric mucus thickness was measured by histology.

Results: Pronase reduced mean gastric mucus thickness from 162 to 30 μm ($p < 0.001$), reduced coverage from 100 to 60% and caused some fissuring of the epithelial cell layer. There was a 66% increase in gastric clearance of metronidazole (control = 0.087 ± 0.014 mL/min, pronase = 0.145 ± 0.041 , $n = 17$, $p = 0.005$). Gastric clearance of amoxicillin increased four-fold (control = 0.0029 ± 0.0019 , pronase = 0.0120 ± 0.0038 , $n = 16$, $p < 0.001$). However there was a 40% reduction in the gastric clearance of clarithromycin (control = 0.129 ± 0.031 , pronase = 0.082 ± 0.018 , $n = 15$, $p = 0.003$).

Conclusions: Pronase damages the gastric mucus layer and epithelial integrity suggesting that these are barriers to the gastric transfer of amoxicillin and metronidazole. This may account for the improved eradication rates with pronase. Gastric mucosal damage reduces the clarithromycin secretion rate, suggesting that a different transport process is involved for this larger, more lipophilic molecule.

053 VALIDATION OF A RISK STRATIFICATION IN ACUTE UPPER GASTROINTESTINAL HAEMORRHAGE

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Aim: Acute upper gastrointestinal haemorrhage has an incidence of approximately 100 per 100,000 per year and an event related mortality of up to 14%. Accurate identification of risk of mortality prior to endoscopy would allow focused treatment of high risk patients.

Method: Over a 3-year period, all consecutive patients admitted to our institution with acute upper GI haemorrhage were prospectively stratified and followed up. Patients were stratified into the highest risk group for which they possessed at least 1 putative risk factor (*high risk*: recurrent bleeding, persistent tachycardia ($>100/\text{min}$), history of oesophageal varices, systolic BP $<100\text{mm Hg}$, coagulopathy, thrombocytopenia, postural hypotension ($>20\text{mm Hg}$) whilst taking negative chronotropes; *intermediate risk*: age >60 years, haemoglobin $<11\text{g/dl}$, co-morbidity, melaena, alcohol (excessive recent or chronic), NSAIDs, previous GI bleed or peptic ulceration, abnormal LFTs, postural hypotension ($>10\text{mm Hg}$), systolic BP $>20\text{mm Hg}$ below patient's normal; *low risk*: none of the aforementioned factors).

Results: 1349 episodes occurred during the study period (incidence of 100 per 100,000 per year). 2-week mortality was 84 (6.2%) overall with 66 (11.8%) of 561 high risk, 18 (2.5%) of 717 intermediate risk and 0 (0%) of 71 low risk. This was significantly higher in the high risk group than intermediate ($p < 0.001$) or low risk ($p = 0.002$). Significantly more high risk than intermediate risk patients rebled (250 vs 16), underwent surgical intervention (27 vs 9), required transfusion (239 vs 234) and required central venous monitoring (130 vs 0) (all $p < 0.001$). None of these end-points occurred in low risk patients.

Conclusions: This risk stratification was easily applied prior to endoscopy by junior medical staff at a single institution. It identified groups at particularly high and low risk of mortality and other adverse end-points following haemorrhage. It is simple and rapidly applied and might be useful both to hospital physicians and general practitioners, allowing more intensive management of those at highest risk and, potentially, outpatient management of those at lowest risk.

054 ASSESSING CYCLIN D1 & p53 AS MARKERS OF MALIGNANT POTENTIAL IN BARRETT'S OESOPHAGEAL ADENOCARCINOMA USING TISSUE MICROARRAYS

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Background/aims: Molecular markers of malignant potential may hold the key to identifying high-risk individuals leading to more efficient and effective surveillance programmes in Barrett's Oesophagus. Our aims were to see if tissue microarray technology could be used to a) determine p53 expression in the Barrett's / carcinoma sequence and b) see if the cell cycle regulator, cyclin D1, has a prognostic significance.

Patients/methods: We have constructed microarrays using paraffin embedded tissue at several different stages of cancer development in 114 patients (95 men, 19 women) who had undergone resection over the last 10 years for Barrett's oesophageal adenocarcinoma (BOA). Tissue cores of squamous epithelium, gastric epithelium, Barrett's intestinal metaplasia (BIM), different grades of dysplasia, BOA and positive lymph nodes for each patient were taken wherever possible. Age at resection was 39–83 years (mean age 63 years). Resection staging was 17.5% T1, 14.1% T2, 68.4% T3, 58.8% N1 and 6.1% M1. Microarray sections were then stained using p53 and cyclin D1 antibodies.

Results: For p53 we found positive stained cores in 1.6% of histologically normal epithelium (2 of 122), 6.7% of BIM (3 of 45), 56% of dysplasia (42 of 75), 43.1% of BOA (44 of 102) and 49.1% of positive lymph nodes (28 of 57). For cyclin D1 we found positive stained cores in 100% of BIM (46 of 46), 93.3% of dysplasia (70 of 75), 88.9% of BOA (88 of 99) and 79.6% of positive lymph nodes (43 of 54).

Conclusions: As p53 positive staining does not significantly precede the onset of dysplasia it is not a clinically useful marker of malignant potential in patients with Barrett's oesophagus. This data

does however support Cyclin D1 as a candidate marker of malignant potential. These results agree with a recently published study showing 92% of patients (11 of 12) with BOA overexpressed cyclin D1 at some point before the onset of BOA. This marker warrants further study to assess any possible clinical role in identifying high-risk patients in surveillance programmes.

055 IMPORTANCE OF METAPLASTIC SUBTYPES AND SQUAMO-COLUMNAR CROSS-TALK IN THE AETIOPATHOGENESIS OF INFLAMMATORY AND MALIGNANT COMPLICATIONS IN BARRETT'S OESOPHAGUS (BE)

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We have previously demonstrated an inflammatory gradient in long segments of BE. Acute inflammation occurs proximally with oesophagitis at the neo squamo-columnar junction, whereas anti-inflammatory cytokines predominate distally. We investigated whether the proximal-distal differences occur due to the metaplastic subtypes or the interaction between the squamous and columnar cell types.

Methods: Mucin histochemical staining was performed to identify areas of gastric compared with specialized intestinal metaplasia (SIM types I, II, III), (multiple samples from n=35 patients) and p53 overexpression in the proximal and distal segment using immunohistochemistry (n=26). A retrospective study was performed to determine the site of origin of adenocarcinoma/high-grade dysplasia (n=32). For squamo-columnar interactions we used competitive RT-PCR to quantify IL-1 β , IL-8 and TGF- β expression in cultures of squamous (OE-21) and Barrett's (TE7) carcinoma cell lines separately and in a co-culture system (OE-21+TE7).

Results: There was no difference in the amount of SIM vs. gastric metaplasia along the BE segment ($P>0.5$). Type III intestinal metaplasia was the predominant subtype in patients with dysplasia ($P<0.05$). P53 expression was significantly increased in the distal compared with the proximal segment in patients with >8 cm BE segments ($P=0.01$). The majority of adenocarcinomas occurred in the distal end of BE (distal: proximal ratio, 6:1). Levels of TGF- β were increased by at least 3-fold in the co-cultures compared with individual cultures; whereas IL-8 and IL-1 β levels were increased by 70% in squamous (OE-21) and co-cultures compared with the Barrett's (TE7) cultures.

Conclusions: Type III SIM and p53 overexpression correlate with dysplasia which predominates in the distal BE segment. Increased cytokine expression in the co-cultures suggests that cellular cross-talk may be important for the development of proximal inflammatory complications in BE.

056 "ROUTINE"CHROMOENDOSCOPIC IMAGING IN THE UK-IS IT WORTHWHILE?

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Introduction: Gastric cancer is the second most common cause of cancer death world-wide and the fourth commonest in the UK in men after lung, colorectal and prostate, yet the detection rate of early gastric cancer in the UK remains poor when compared to Japan. This may be due to a variety of factors but the difference in endoscopic technique between East and West may have a significant part to play in this discrepancy.

Aims: The aim of this study was to see if using "Japanese style" endoscopic techniques in the UK (with methylene blue contrast dye spraying and routine use of buscopan) could improve the detection rate of Early Gastric Cancer (EGC) in symptomatic patients over 50 years of age attending for open access endoscopy.

Methods: Each patient attending for open access endoscopy who was over the age of 50 was asked to participate in the study. Those that agreed underwent a conventional upper GI endoscopy, followed by chromoendoscopy using methylene blue. Any new findings seen were recorded and stored digitally using a Sony mini-disc recorder.

Results: 500 patients were recruited between October 1999 and October 2000. Examinations were performed on 498 patients (2 examinations were abandoned - 1 with food in the stomach, 1 with a pharyngeal pouch). A total of 483 patients had dye sprayed. The mean age was 62.7 years (median 61.5). The ratio of M: F was 44:56. Overall findings were oesophagitis in 153 patients (31.7%), gastric ulcers

in 15 (3%) and duodenal ulcers in 11 (2%). Polyps were identified in 17 patients initially but after dye spraying this rose to 33 (7%). Minor mucosal abnormalities were common but abnormal areas thought suspicious enough to warrant a targeted biopsy were seen in only 13 patients initially; this rose to 40 after dye spraying (8%). 3 gastric cancers were found (0.6%) of which 1 was an Early Gastric Cancer (30%). Prior to the use of methylene blue this lesion had a "gastritis"-like appearance but after spraying a depth to the area could be appreciated. The mean time taken to perform the chromoendoscopies was 13.8 minutes.

Conclusions: Routine chromoendoscopy takes around 15 minutes to perform with no demonstrable increase in the detection of gastric cancer. However, the technique is useful for delineating a lesion already detected using conventional means. These early results do not support the routine use of chromoendoscopy.

057 THE ROLE OF ENDOSCOPIC ULTRASOUND (EUS) IN THE PRE-OPERATIVE STAGING OF HIGH-GRADE DYSPLASIA AND ADENOCARCINOMA ARISING WITHIN A SEGMENT OF BARRETT'S OESOPHAGUS

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Introduction: At the current time, curative treatment for adenocarcinoma arising in Barrett's oesophagus requires an oesophagectomy. Since oesophagectomy is associated with significant morbidity and mortality, accurate pre-operative information is essential in order to select patients with curable disease. Available oesophageal staging methods are CT scanning, endoscopic ultrasound (EUS) or laparoscopic staging. EUS is not routinely available in District General Hospitals and patients with non-dysplastic Barrett's oesophagus have a thickened mucosal segment on EUS which may make accurate tumour staging difficult. The aim of this study was to compare the staging information obtained from spiral CT scanning and EUS, with the stage of the resected specimen.

Methods: Nine patients who had staging information available from an EUS and who also had an oesophagectomy for Barrett's adenocarcinoma were identified. At endoscopy all of these patients had Barrett's oesophagus and 8/9 had a macroscopically visible cancerous lesion. The results of their pre-operative EUS was compared to that of their staging CT and the histology of the surgically resected specimen.

Results: Pre-operative histology indicated adenocarcinoma in 6 of the patients and high grade dysplasia in 3. Post operative histology revealed evidence of intramucosal carcinoma in 2 of the latter. EUS over staged the lesion in 4 patients. 3 had intramucosal disease incorrectly staged as invasive disease (two as T3, N0 and one as T2, N0). The fourth had lymphadenopathy incorrectly identified. The lesion was under staged by EUS in 4 patients. Nodal disease (T3, N2) was not recognised in one. The other lesions were all down graded by one tumour (T) stage. 6/9 had spiral CT prior to their operation. Only 1 CT correctly identified invasive oesophageal disease and 2 patients had lymphadenopathy that was not detected.

Conclusions: EUS is more sensitive than spiral CT scanning. Although the EUS was not accurate for T stage, N staging was accurate in 7/9 of patients. Only one patient had an inappropriate operation on the basis of their EUS. Since, nodal status is an important predictor of 5 year survival EUS is useful for selecting patients suitable for oesophagectomy.

058 TREATMENT OUTCOMES FOR CARDIO-OESOPHAGEAL CANCER IN THE WEST MIDLANDS

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We have performed a region wide study of patients presenting with carcinoma of the oesophagus and cardia. Our retrospective audit involved case-note review of 3661 patients within the West Midlands over the five-year period from 1992-96.

The mean age was 69.8 yrs, with a male to female ratio of 2:1. Oesophageal tumours were split equally between adeno- and squamous cell carcinomas, whilst those at the cardia were almost exclusively adenocarcinomas. Sixty percent of oesophageal tumours were located in the lower third, while 33% were in the middle third. In 18% of resected cases the initial anatomical site of tumour at diagnosis was subsequently found to be inaccurate.

Most patients underwent more than one treatment modality and the vast majority had advanced disease at presentation. Five-year survival was 20% in patients undergoing resection. Other treatment modalities did have long-term survivors, but these were small in number.

The table summarises the outcomes of the various primary treatment modalities.

Abstract 58, Table 1

	Number	Mean age	30 day mortality	1-year survival
No treatment	522	74.6	36%	7%
Ablation	242	76.1	12%	10%
Dilatation	425	73.4	19%	11%
Intubation	374	72.3	18%	5%
Radiotherapy	571	71.2	2%	23%
Chemotherapy	135	61.8	4%	16%
Resection	1125	63.8	10%	55%

The data from this audit confirms the poor outlook for patients presenting with cardio-oesophageal cancer, but may provide a baseline for future changes in health care delivery for upper GI cancer in the UK.

059 GASTRIN MEDIATED EXPRESSION OF P53 IN AGS GASTRIC CANCER CELLS

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Introduction: Gastrin is an important trophic hormone for malignant and normal gastric mucosal, and the trophic action of gastrin has been shown to act in an autocrine and paracrine manner in cell culture. Animal models of gastric carcinogenesis have implicated the overexpression and mutation of p53 in response to hypergastrinaemia. p53 mutations are common in gastric cancer. Does gastrin have an effect on p53 in human tumours.

Methods: AGS Gastric cancer cells were obtained from ECACC, and grown in Ham's F12 medium supplemented with 10% FCS. For time course experiments cells were plated out onto 100mm tissue culture plates, and grown to 50% confluence, cells were treated with 0.2µg/l Gastrin 17 (Sigma) in serum free and serum supplemented medium. Cells were harvested at 0, 6, 12, 24, and 48 hours. For dose response experiments cells were treated with 0µg/l, 0.2µg/l, 0.4µg/l, 0.6µg/l, and 1.2µg/l and harvested at 24 hours. Cells were lysed with a urea based lysis buffer, protein concentration estimated, and separated using SDS PAGE electrophoresis. Protein was transferred to a nitrocellulose membrane overnight. The membrane was probed with DO-1 (anti-p53) and Ab1 (anti-p21) and detected using ECL. For RT-PCR, total RNA was extracted using a total RNA extraction kit (Quiagen), reverse transcription (RT) performed using superscript RT (Quiagen) and cDNA amplified using Hotstar Taq (Quiagen) with primers for Gastrin and the Gastrin/CCK-B receptor. PCR product was separated on a 2% agarose gel and visualised with ethidium bromide staining.

Results: Gastrin caused an increase in p53 expression peaking at 12hours, no alteration in p21 levels were noted. This occurred in a dose response with a maximal expression of p53 at a concentration of 0.6µg/l. RT-PCR detected a product for Gastrin but not for the Gastrin receptor.

Summary: Gastrin seems to have a relationship with p53 expression and may be implicated in generating a fertile field for carcinogenesis to occur.

060 A 9 YEAR RETROSPECTIVE STUDY OF UPPER GI ADENOCARCINOMA. HOW MANY CANCERS ARE WE MISSING

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Background: The detection rate of Early Gastric Cancer (EGC) in the UK remains low despite the widespread availability of gastroscopy. Previous research has suggested that treatment with acid suppressing medication (AST) prior to gastroscopy can lead to cancers being missed at endoscopy.

Aims: The aim of this large retrospective study is to identify where improvements can be made in the diagnosis of adenocarcinoma and to identify the potential for making earlier diagnosis.

Methods: All upper GI adenocarcinomas diagnosed in South Tees Health District (population ~ 350,000) were identified from the computerised pathology database. The pathology and GP records were then reviewed and analysed using EpiInfo.

Results: The total number of patients identified was 618 (for the period April 1991- January 2000); to date 102 patients' notes have been analysed. 94% were adenocarcinoma of which 26% were oesophageal and 74% were gastric. 6% were squamous carcinoma (mis-coded on the pathology computer). The M: F ratio is 63.5:36.5 and the mean age is 70.2 years (range 43-91). The symptoms at time of diagnostic investigation were (i) anaemia/weight loss/dysphagia in 55.2% (ii) epigastric pain in 31.3% (iii) dyspepsia/reflux/heartburn in 9.4% and (iv) haematemesis/melaena in 4.2%. Of the 96 patients with adenocarcinoma 55% had AST between the 1st GP consultation and diagnosis and in 57% this was initiated at the 1st visit. Overall the GP suspected a cancer diagnosis in 24% of cases. For those treated prior to gastroscopy the mean time from 1st GP consultation to diagnosis was 17.1 weeks compared to 9.2 weeks in those given no treatment. Of the 43 patients who had no AST prior to the diagnostic investigation only 1 (2.3%) had had a previous OGD within 3 years of diagnosis, whereas of the 53 who had been prescribed AST prior to the diagnosis 18 (34%) had had a previous OGD (p=0.0001). Overall, 27% of the cancers had had a previous upper GI investigation within 3 years of the diagnostic investigation, of which 73% were OGD and 23% were barium studies. 40% had had a previous upper GI investigation more than 3 years from the diagnostic OGD.

Conclusion: Although this is preliminary data, it shows that 41% of patients did not have alarm symptoms at diagnosis. Also 55% of patients were treated with AST prior to the diagnostic OGD increasing the mean time from 1st GP consultation to diagnosis from 9.2 to 17.1 weeks. It seems likely that 34% of cancers were not diagnosed at the time of their first investigation and therefore the potential for improving the detection of EGC is significant.

061 ABSENCE OF TOLL LIKE RECEPTOR 4 (TLR4) EXPLAINS ENDOTOXIN HYPORESPONSIVENESS IN HUMAN INTESTINAL EPITHELIUM

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Introduction: The Toll protein in *Drosophila* regulates dorsal ventral patterning during embryogenesis and participates in antibacterial and antifungal host defense. Mammalian homologs are termed Toll like Receptors and in humans, six have been cloned (TLR1-6). They are characterised by extracellular leucine rich repeats and a cytoplasmic domain similar to the Interleukin 1 receptor. Both TLR2 and TLR4 recognise various bacterial cell wall components including lipopolysaccharide (LPS). This results in activation of the NFκB pathway. Peripheral blood lymphocytes (PBLs) express both TLR2 and TLR4. We hypothesise that the expression of TLR2 and TLR4 in human intestinal epithelial cells differs to PBLs because of the abundance of LPS in the intestinal lumen.

Methods: Epithelial cells were isolated from Caco-2 cells (a human intestinal carcinoma cell line), fetal gut explants and small bowel resection specimens using Hanks/EDTA solution. Peripheral blood lymphocytes (PBLs) were used as positive controls. RNA was isolated by TRIzol method. Standard RT-PCR examined TLR2 and TLR4 mRNA expression. NFκB expression was determined using a luciferase reporter assay.

Results: TLR2 mRNA was highly expressed in PBLs and was present in all human intestinal epithelial cells. TLR4 mRNA was detected only in PBLs. TLR4 is not present in epithelium from children with inflammatory bowel disease. In Caco2 cells significant NFκB activation in response to LPS only occurred in the presence of TLR4.

Conclusion: TLR2 mRNA, but not TLR4 mRNA, is present in normal human intestinal epithelial cells. TLR4 is not directly involved in inflammation of the epithelium. Although TLR2 is normally present in the epithelial cell, it plays a limited role in inflammation. It may be activated in conditions where bacterial cell wall concentrations within the intestine are pathologically high.

062 INCREASED EXPRESSION OF PRO-IL-18 BY INTESTINAL EPITHELIAL CELLS INFECTED WITH CRYPTOSPORIDIUM PARVUM

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Introduction: Cryptosporidiosis is an important cause of diarrhoea world-wide. The causative organism, *C.parvum*, is an intracellular parasite that infects the gastrointestinal epithelium. The development of a Th1-mediated immune response and in particular enhancement of IFN γ production is critical in the control of the parasite. Epithelial cells may function as immune sensors of infection by producing cytokines including the Th1 inducing cytokine IL-18. We therefore explored the potential of *C.parvum* to modulate IL-18 production by enterocytes using an established in vitro model of infection.

Methods: HCT 8 and Caco-2 cells were grown to confluence in 24 well plates and infected with either viable or heat-inactivated purified *C.parvum* sporozoites (0.05–2x10⁶ sporozoites/well) in some experiments cells were pre-treated with IL-18 (2–200ng/mL) for 24h prior to infection. Forty eight hours after infection protein expression of mature and pro-IL-18 in cell lysates of infected and uninfected cells was determined by Western blotting using an anti-IL-18 antibody. IL-18 mRNA expression was also quantified by competitive RT-PCR in infected and uninfected cells 24h post-infection. Infection in IL-18 pre-treated cells was quantified by immunofluorescence microscopy using an anti-*C.parvum* antibody and compared to untreated controls.

Results: Forty eight hours post-infection pro-IL-18 protein expression was increased in infected cells compared to uninfected control cells or cells inoculated with heat-inactivated parasites and this increase was related to initial parasite inoculum. No concomitant rise in the expression of mature IL-18 was observed. IL-18 mRNA induction paralleled the increase in pro-IL-18 protein expression. At 24h post-infection a 30 fold increase in IL18 mRNA was observed in infected HCT 8 cells compared with uninfected control cells or cells infected with killed sporozoites. Infection was inhibited in IL-18 pre-treated cells, maximal inhibition was 31.1% $\pm$ 7.1 ($p < 0.001$).

Discussion: Our findings indicate that *C.parvum* may induce both expression of IL-18 mRNA and pro-IL-18 by enterocytes, and that recombinant IL-18 may inhibit infection in an in vitro model. Production of mature IL-18, which is dependent on the activation of caspase 1 does not occur. We speculate that *C.parvum* infection in vivo may activate caspase 1 in enterocytes by an unknown mechanism resulting in production of mature IL-18. (RCGP is a Wellcome Trust Training Fellow).

063 BIOACTIVITY OF PEPTIDES HOMOLOGOUS TO THE COELIAC DISEASE-SPECIFIC DOMINANT T CELL EPITOPE

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Gluten challenge in HLA-DQ2+ coeliac disease (CD) initially induces T cells in peripheral blood specific for a single A-gliadin peptide (residues 57–73) modified by transglutaminase (tTG) (Anderson et al Nat. Med. 2000; 6:337–42). Gliadin-specific intestinal T cell clones have allowed characterization of A-gliadin 57–68 QE65, and several other gliadin peptides as T cell epitopes. If the immune response in coeliac disease is truly focused on a single epitope it might be possible de-toxify wheat by genetic modification or develop peptide therapeutics.

Aim: To determine the specificity of the initial T cell response in coeliac disease for gliadin and non-gliadin peptides.

Methods and results: HLA-DQ2+ CD subjects (n=8 for each peptide tested) on gluten free diet consumed bread (200g/d) for 3 days; interferon gamma (IFN γ) Elispot assays using peripheral blood mononuclear cells (PBMC) drawn on day 6 were used to compare the bioactivity of peptides. The core 5 aminoacid sequence (residues 64–68, PELPY) of the dominant epitope A-gliadin 57–73 QE65 was defined using variants containing lysine substituted for each aminoacid in turn. 16 different gliadin sequences from 25 gliadin proteins contained the sequence PQLPY, and none PELPY (the tTG-modified product of PQLPY). None of the gliadin polymorphisms were bioactive without treatment by tTG, or substitution of Q65 for glutamate (E). Bioactivities of five tTG-treated or QE65-substituted gliadin polymorphisms were comparable to

A-gliadin 57–73 QE65, but 4 were less than 10% as bioactive even with tTG treatment. In addition, 9 non-gliadin sequences containing PQLPY were tested, none was bioactive but 7/9 were susceptible to tTG modification (XPQLPYX – XPELPYX). Other gliadin and glutenin peptides defined as epitopes for T cell clones by others were either non-bioactive or suboptimal agonists using PBMC after gluten challenge in CD.

Conclusion: The sequence PQLPY is ubiquitous and amenable to tTG modification. T cells induced with gluten challenge in CD recognize multiple gliadin polymorphisms of A-gliadin 57–73 after tTG modification. “De-toxification” of wheat by knock-out of a single gliadin is unlikely to succeed.

064 THE EFFECT OF PROBIOTICS ON BACTERIAL TRANSLOCATION AND SEPTIC MORBIDITY IN ELECTIVE SURGICAL PATIENTS

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Aims: Bacterial translocation occurs in surgical patients and may account for postoperative sepsis. Many factors are thought to influence the prevalence of translocation, one of which is the luminal density and composition of the gut microflora. The aim of this study was to assess the effect of the probiotic *Lactobacillus plantarum* 299v (Provia) on the incidence of bacterial translocation and septic complications in elective surgical patients.

Methods: In this prospective trial, surgical patients awaiting major GI resection were randomised to receive an oral preparation containing *Lactobacillus plantarum* 299v for one week preoperatively and compared with a control group. All patients were taking a normal diet until the date of surgery. Bacterial translocation was assessed by the culture of mesenteric lymph nodes and serosal biopsies. Nasogastric aspirates were taken to establish gastric colonisation with enteric organisms. All septic morbidity was documented.

Results: 129 patients were entered into the study.

Abstract 64, Table 1

	Provia Group (n=64)	Control Group (n=65)	P
M:F Ratio	39:25	36:29	
Median age (IQR)	68 years (58-74)	69 years (58-77)	
Bacterial translocation	7 patients (11.8%)	7 patients (11.8%)	>0.05
Gastric colonisation	6 patients (11.0%)	8 patients (15%)	>0.05
Septic complications	7 patients (11.8%)	10 patients (15.3%)	>0.05

Conclusions: *Lactobacillus plantarum* 299v administration in elective surgical patients does not alter bacterial translocation rates or subsequent septic morbidity. The use of a preoperative probiotic had no effect on the incidence or nature of gastric colonisation.

065 EARLY ENTERAL FEEDING VERSUS ‘NIL BY MOUTH’ FOLLOWING GASTROINTESTINAL SURGERY: SYSTEMATIC REVIEW AND META-ANALYSIS

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Early enteral feeding after gastrointestinal surgery may be of benefit, however, a period of starvation (‘nil by mouth’) is still routine practice. We performed a systematic review of the effectiveness of early enteral feeding. Systematic review and meta-analysis of randomised trials comparing any type of enteral feeding within 24 hours of surgery with management by ‘nil by mouth’ in elective gastrointestinal surgery. Three electronic databases were searched, reference lists checked and letters requesting details of unpublished trials sent to pharmaceutical companies. Anastomotic dehiscence, infection of any type, wound infection, pneumonia, intra-abdominal abscess, length of hospital stay and mortality. 11 studies met the inclusion criteria. Feeding directly into the small bowel was used in the intervention group in six of the studies and oral feeding in five. Early feeding reduced the risk of anastomotic dehiscence (RR 0.53, 95% CI 0.26 to 1.07, P=0.077), the risk of any type of infection (RR

0.72, 95% CI 0.53 to 0.98, $P=0.036$), and the mean duration of hospitalisation (reduction by 0.84 day, 95% CI 1.33 to 0.36 day, $P=0.001$). Risk reductions were also seen for wound infection, pneumonia, intra-abdominal abscess and mortality but these were not statistically significant ($P>0.10$). The risk of vomiting was increased among patients fed early (RR 1.27, 95% CI 1.01 to 1.61, $P=0.045$). Early feeding appears to be of benefit. An adequately powered trial is required to confirm or refute the benefits seen in small trials.

066 THE EFFECT OF GLUCAGON-LIKE PEPTIDE-2, EPIDERMAL GROWTH FACTOR AND GLUTAMINE ON INTESTINAL GROWTH

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Background: Glucagon-like peptide 2 (GLP-2), epidermal growth factor (EGF) and glutamine (gln) stimulate growth of the intestine in the total parenteral nutrition (TPN) rat model. However, in this model the interaction of GLP-2 with EGF or gln has not been investigated.

Aims: To determine whether EGF or gln has a synergistic effect on growth of the intestine with GLP-2.

Methods: Rats were established on TPN. The treatment groups were as follows; 20 mcg/day of GLP-2, 20mcg/day of EGF, 20mcg/day of GLP-2 plus EGF, 2% gln, and 2% gln plus 20mcg/day of GLP-2. The small intestine and colon were weighed. Tissue was obtained from the jejunum, ileum and colon. This was microdissected to determine the changes in metaphase arrest scores.

Results: The mean ($\pm$ SEM) small intestinal weight (g) in the TPN, GLP-2, EGF, GLP-2/EGF, gln and gln/GLP-2 groups were 1.7($\pm$ 0.02), 3.1($\pm$ 0.07), 2.5($\pm$ 0.04), 3.8($\pm$ 0.1), 1.9($\pm$ 0.13) and 2.8($\pm$ 0.11) respectively (all $p<0.001$ compared to TPN group, except gln group). The mean ($\pm$ SEM) colonic weight(g) for the above groups were 0.44($\pm$ 0.01), 0.45($\pm$ 0.02), 0.72($\pm$ 0.02), 0.75($\pm$ 0.03), 0.50($\pm$ 0.03) and 0.50($\pm$ 0.04). Two way ANOVA without interaction demonstrated a significant effect by gln on colonic weight ($P<0.05$). The mean metaphase arrest scores/crypt in the 10% small intestine for TPN, GLP-2, EGF, GLP-2/EGF, gln and gln/GLP-2 groups were 22.7($\pm$ 1.04), 52.64($\pm$ 3.07), 38.8($\pm$ 2.41), 77.8($\pm$ 4.52) 22.9($\pm$ 4.1) and 49.5($\pm$ 5) (All $p<0.001$ compared to TPN, except gln group).

Conclusion: GLP-2 and EGF have additive effects on growth of the small intestine. Furthermore gln does not augment the growth of the intestine stimulated by GLP-2. However there is a modest effect of gln on colonic growth.

067 TNF- α INDUCES β -CATENIN/TCF MEDIATED TRANSCRIPTION: OPPOSING ACTIONS OF MAPK AND NF κ B PATHWAYS

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Neoplasia and epithelial remodelling are both features of chronic inflammation. We have previously shown that TNF- α stimulation of the epithelial cell line Caco-2 results in increased β -catenin / TCF mediated transcription. β -catenin is predominantly bound to the adhesion molecule E-cadherin, with free cytoplasmic β -catenin being rapidly degraded. Undegraded β -catenin migrates to the nucleus, binds TCF transcription factors which together induce the transcription of a growing number of oncogenes including c-myc and cyclin D1 (this is termed β -catenin / TCF mediated transcription). The inflammatory cytokine TNF- α can act via several intracellular signalling pathways, including the MAP Kinases (ERK, p38 and JNK) and NF κ B. This study examines the intracellular pathways involved in TNF- α regulation of β -catenin / TCF mediated transcription. The TOPFLASH luciferase reporter is employed, and in this system luciferase activity is a measure of β -catenin / TCF mediated transcription.

Luciferase activity following TNF- α stimulation was assessed in the presence or absence of inhibitors of ERK, p38 and NF κ B activation. There was a significant (2.7 fold; $p<0.05$) increase in the relative levels of luciferase activity following stimulation with TNF- α . This was reduced to baseline (pre TNF- α stimulation) levels by pre-incubating with p38 or ERK inhibitors. However, pre incubation with the NF κ B inhibitor acted to increase the luciferase activity over that seen with TNF- α alone (8 fold increase versus 2.7 fold increase). Thus TNF- α acts to increase β -catenin / TCF mediated transcription and this is

dependant on ERK and p38 activation but not on NF κ B activation, which appears to be acting in an opposing manner. This study indicates a mechanism whereby the inflammatory cytokine TNF- α can act to regulate β -catenin / TCF mediated transcription, the final targets of which are oncogenes.

068 NOVEL POLYMORPHISMS IN THE BETA 7 INTEGRIN GENE (ITGB7): FAMILY BASED ASSOCIATION STUDIES IN IBD

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Background: Linkage studies from five groups worldwide have confirmed the presence of an inflammatory bowel disease (IBD) susceptibility locus on chromosome 12q. ITGB7, a positional candidate gene within this region, is involved in lymphocyte homing to the gut and retention of intra-epithelial lymphocytes. Monoclonal antibodies to alpha 4 beta 7 integrin have been shown to ameliorate colitis in animal models. No polymorphisms in ITGB7 had been reported and therefore we screened this gene in order to identify markers to test for association. In order to overcome potential false positive results from a case control study, polymorphisms were genotyped in IBD families and the transmission disequilibrium test (TDT) was used to assess association.

Aims: To screen ITGB7 for polymorphisms, and carry out association testing of common or functional polymorphisms in IBD families.

Methods: Genomic sequence was obtained for the whole gene and promoter region by direct sequencing of the products of inverse PCR and PCR between exons. PCR fragments covering all 16 exons and 1.7kb of 5' promoter region were designed and analysed for polymorphisms in 24 individuals by denaturing HPLC (Transgenomic Wave). Samples showing heterozygote traces were sequenced to verify the SNP. PCR-RFLP assays were designed for each SNP and allele frequencies were tested in 90 healthy controls. Common alleles (frequency $\geq 10\%$) and potentially functional polymorphisms were genotyped in 567 trios from 464 IBD families. A permutation based probability test was used to calculate association independent of linkage (Aspex).

Results: 14 SNPs were identified and two common intronic and two amino acid changing SNPs were genotyped. Data were available from 102 multiply affected families and 362 simplex families containing 254 ulcerative colitis (UC), 13 indeterminate colitis and 300 Crohn's disease (CD) trios. No significant TDT results were obtained with any SNP for the IBD, UC or CD phenotype.

Conclusion: The ITGB7 gene is unlikely to be involved in IBD susceptibility and therefore future studies on chromosome 12 should focus on other positional candidate genes.

069 AUDIT OF ANTI-TNF α ANTIBODIES IN CLINICAL PRACTICE

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Introduction: Human/mouse chimeric monoclonal antibodies directed against tumour necrosis alpha (TNF α) is becoming an established treatment for steroid resistant and fistulating Crohn's disease (CD). Although the efficacy has been shown in clinical trials, the financial implications often limit its use and there is little data regarding the impact in clinical practice.

Aims: We therefore aimed to audit the clinical effectiveness of the use of Anti TNF α (Infliximab, Centrocort, USA) in the treatment of Crohn's disease and other gastrointestinal conditions in our institutions.

Methods: We prospectively audited the use of Infliximab in both institutions. Data was collected regarding demographic and disease details, and the indication for treatment was confirmed. Clinical disease activity was assessed by the Harvey-Bradshaw index and blood was taken for inflammatory parameters, complement fractions C3 and C4 and double stranded DNA. All patients received an infusion of Infliximab at a dose of 5mg/Kg over 4 hours. The patients were then followed prospectively for 12 weeks and categorised as to whether they had responded or not. If they had responded they were followed until relapse or the end of the 12-week period. A response was defined as improvement in well being with a reduction in steroid dose.

Results: 29 patients received infusions of Infliximab between February 1999 and September 2000. There were 16 females and 13 males with a median age of 35 years (17–68 years). Indications for administration were chronic active steroid resistant CD in 21 patients, fistulating Crohn's disease in 4, resistant pyoderma gangrenosum in 1, refractory pouchitis in 1 and refractory coeliac disease in 2. 15 of the CD patients have undergone previous surgery and 13 had associated perianal disease. 11 were established on immunosuppressives at the time of the infusion. The median dose of Infliximab was 303 mg (range 200–500 mg) and the only adverse event was headache in 3 patients. Follow up is currently available in 23 patients. Of the 23 patients 14 (61%) had a response when assessed at 4 weeks post infusion. Of the 9 that did not respond, 3 had surgical resections and 6 were managed medically. Of the 14 that responded when assessed at 12 weeks 1 had a surgical resection and 3 more had relapsed. The frequency of perianal disease was significantly lower in the group that responded when compared to those that did not ($p < 0.05$). There were no other differences between the groups.

Conclusions: The response rates to Infliximab in our group are comparable to those seen in clinical trials. Despite the cost it remains a useful adjunct to treatment in this otherwise difficult group of patients. Our data suggests that patients with perianal disease respond less well than those patients without.

070 NEUTROPHIL DEFICIENCY DURING ACUTE INFLAMMATION IN INFLAMMATORY BOWEL DISEASE

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Hypothesis: In Crohn's disease (CD) and ulcerative colitis (UC) there is a reduced neutrophil influx during the acute inflammatory response. This may be due to a deficiency in the mediators of acute inflammation.

Aim: i) To assess neutrophil migration into cantharidin induced skin blisters. ii) To assay mediators of acute inflammation in the blister fluid.

Methods: Patients with inactive CD ($n=14$; 5 male; av. 49.8 years (S.D. 20.5) and inactive UC ($n=11$; 6 male; av. 45.1 years (S.D. 12.1) and non-inflammatory controls consisting of medical students (C) ($n=16$; 12 male; av. 22.5 years (S.D. 3.0) were recruited. Cantharidin (0.1% in 25 µl acetone) was applied to 0.8 cm² paper discs onto the forearm, covered with parafilm and an adhesive dressing. 24 hours later the blister fluid was removed. The cellular composition of duplicate blisters was counted microscopically and the average result recorded. Flow cytometry using anti-CD16 and anti-CD14 antibody labelling together with light scatter properties were used to quantitate neutrophils and monocytes/macrophages respectively. Chemokines (interleukin [IL]-8, epithelial cell-derived neutrophil attractant [ENA]-78 and growth-regulated oncogene [GRO]-α) and histamine were measured by ELISA.

Results: Blister volume was significantly lower in CD than in C ($p < 0.05$), as was the total cell influx per blister ($p < 0.01$) and the cell influx after adjustment for blister volume (cells/ml; $p < 0.05$). None of these parameters were significantly reduced for UC. The proportion of neutrophils within each blister was significantly lower in both CD and UC compared to C (both $p < 0.003$). No significant difference was observed for the monocyte/macrophage population for either CD or UC when compared to C; however this population was slightly raised in CD. Both ENA-78 and GRO-α were significantly reduced in CD compared to C ($p < 0.01$ and $p < 0.05$ respectively). Only ENA-78 was significantly reduced in UC ($p < 0.05$). IL-8 was not significantly altered for either CD or UC compared to C. Histamine levels were increased in UC and reduced in CD compared to C (not significant).

Conclusion: Neutrophil influx into skin blisters is significantly reduced in IBD. This is particularly apparent in CD. This may be accounted for by the reduced production of neutrophil chemokines. The delay in neutrophil migration during acute inflammation in IBD patients may be an aetiopathogenic factor for the onset of chronic inflammation. Supported by NACC. Ethics Committee approved.

071 ASSOCIATION BETWEEN THE LOW PRODUCING INTERLEUKIN-10 ALLELE AND ULCERATIVE COLITIS IN PATIENTS UNDERGOING COLECTOMY

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Background: Interleukin-10 (IL-10) is an important immunoregulatory cytokine. IL-10 gene knock-out mice develop a chronic enterocolitis. Recent studies have demonstrated that inter-individual differences in IL-10 production are in a large part genetically determined. A number of polymorphisms in the promoter region of the gene have been identified and the A to G polymorphism at position -1082 has been associated with increased IL-10 production in vitro.

Aims: To assess the hypothesis that the IL-10 -1082 promoter region polymorphism is associated with susceptibility to UC, a case-control association study was performed in well defined UC patients who had undergone colectomy.

Methods/results: Genotyping for the single nucleotide polymorphism at position -1082 (A to G) in the IL-10 promoter region was performed in 127 patients who had undergone colectomy for UC and 198 anonymous blood donors. Disease diagnosis and extent were confirmed by histology of the resected colon. All individuals were genotyped by 5'-nuclease polymerase chain reaction (PCR) using the PE Biosystems Taqman allelic discrimination system using primers and fluorescent probes.

Abstract 71, Table 1

	N	IL-10 -1082 Genotype			Allele A Carriage	Allele A Frequency
		AA	AG	GG		
UC	127	35	70	22	82.7%	55.1%
Controls	198	43	98	57	71.2%	46.5%

Carriage of the low producing allele (A) was significantly associated with UC ($p=0.02$; Odds ratio = 1.93 (95% CI 1.1–3.4; chi-squared 5.5).

Conclusions: This study in well defined patients support the hypothesis that individuals genetically predisposed to produce less IL-10 have an increased susceptibility to UC.

072 TRANSPORT OF MICROPARTICLES ACROSS HUMAN COLON MUCOSA IN VITRO

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Introduction: Transepithelial transport of microparticles across the intestinal mucosa has been studied in animal models, but there is scant data in humans. Peyer's patches in the small intestine are specialized to transport microparticles, but there is little information on microparticle transport in the colon mucosa. It is generally thought that colonic mucosa is not permeable to large sized particles.

Aim: To demonstrate microparticle transcytosis in cultured human colon mucosa, normal and inflamed with or without lipopolysaccharide (LPS).

Methods: Sigmoid colon biopsies from eight Ulcerative or Crohn's colitis patients and 8 normal were cultured in modified Waymouth's medium with or without LPS of *E. Coli* 055:B55 (50 µg / ml). After 3 h of incubation in a modular incubator with 95% O₂ and 5% CO₂ at 37°C, plain, fluorescence latex microparticles, 2 µm in diameter were added (5.68 X 10⁶ per 0.1 ml). Organ culture was maintained for further 21 h and tissue viability was assessed by BrdU uptake. Fluorescent microparticles were located in 15 µm cryostat sections stained with propidium iodide under epifluorescence and confocal laser scanning microscope. In TEM, location of particles in the cytoplasm was determined. Statistical analysis was done by SPSSPC+ and groups were compared by non-parametric tests.

Results: BrdU uptake in dividing cells confirmed viability of explant tissues in short-term organ culture up to 24 h. Serial optical sections by confocal laser scanning microscope showed that particles were located in the epithelium and lamina propria. Number of particles (per mm²) transcytosed in normal with or without LPS were (mean ± SE): 28 ± 4 vs. 36 ± 5, $p = NS$. In IBD, number of particles

transcytosed without vs. with LPS were (mean $\pm$ SE): 84 ± 11 vs. 232 ± 35 , $p < 0.001$. The number of transcytosed particles in IBD were significantly more ($p < 0.01$) compared to normal with or without LPS.

Conclusion: We have shown for the first time microparticle transport across human colon mucosa. Particles as large as $2 \mu\text{m}$ were transported *in vitro*. More particles were transported across inflamed colon mucosa compared with normal mucosa. LPS augmented particle transport in inflamed mucosa only. The implication of such inert particle transport in terms of amplification of inflammation requires further study. The results also indicate the potential for particulate drug delivery to the colon.

073 AN AUDIT OF OPPORTUNISTIC SCREENING OF PATIENTS PRESENTING WITH LOWER GI SYMPTOMS IN A SINGLE-HANDED GP PRACTICE OVER AN EIGHT YEAR PERIOD

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In recent years, this single handed general practice has referred patients for fiberoptic sigmoidoscopy as an initial investigation when they have presented with symptoms suggestive of a lower gastrointestinal cause, including iron deficiency, or with a strong family history (FH) of colon cancer. The referral indications have been very similar to the present colon cancer referral guidelines. Following sigmoidoscopy, a decision was made about the need for further assessment. The overall outcome was recorded. The audit reviews the data of 175 referrals over 8 years, 1992–99 inclusive. The ages ranged from 20–90 years (mean 58). For 93% of all the patients the duration of symptoms to the time of presentation to the GP was less than 12 weeks (mean 6 weeks). The main reasons for referral were: rectal bleeding (27%), culture negative diarrhoea lasting a minimum of 6 weeks (37%) and abdominal pain (22%). Alternating constipation and diarrhoea occurred in 18% but only 3% of asymptomatic patients were referred on account of a FH despite a newsletter being sent to all patients in the practice. Of these 175 patients having a sigmoidoscopy examination, 58 had a subsequent barium enema and 24 a colonoscopy. Carcinoma was found in 8 patients (4.5%) and colonic polyps in 21 (12%) and in 2 of these the dysplasia was severe. Twelve (7%) patients had colitis +/- proctitis whilst the overall result was considered normal in nearly 50% of those examined. Five of those with carcinoma and 6 of those with polyps were under the age of 60 whilst 5 of those with colitis were over 60. The overall numbers referred for sigmoidoscopy from this practice were readily manageable by the local endoscopy service and were comparable numerically to those undergoing upper GI endoscopy over the same period.

General practitioners should therefore be encouraged to refer within the new cancer guidelines and to take the advantage of opportunistic limited colon assessment in those presenting with symptoms.

074 INTERCOLLEGIATE-BSG NATIONAL COLONOSCOPY (IBNC) AUDIT: EVALUATION OF THE PRESENCE OF ABNORMAL FINDINGS WITH THE INDICATION FOR COLONOSCOPY

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Introduction: Colonoscopy is acknowledged as the gold standard for examining the colon. Demand for colonoscopy continues to increase for diagnosis, therapy and surveillance. As part of the IBNC audit, the primary indication for the colonoscopy and the diagnosis reported following the procedure were recorded. Abnormalities included polyps, diverticular disease, colitis, tumour, previous colorectal resection, strictures, angiodysplasia, melanosis coli, foreign body and "other". A comparison was made between indications and outcomes in 8902 colonoscopies.

Results: Diagnosis was the sole indication in 4333/8902 colonoscopies. The most frequent diagnostic indications are shown with the number of abnormal colonoscopies. Diverticulosis has been separated from other diagnostic categories.

Solely therapeutic colonoscopies were abnormal in 176/189 (93.1%). The most common indication with findings of cancer was bleeding.

Abstract 74, Table 1

Indication	Abnormal colonoscopies/Total colonoscopies within indication (%)	Colonoscopies where diverticular disease is only abnormality / Total colonoscopies within indication (%)	Colonoscopies where abnormality found other than diverticular disease (%)
Abdominal pain	62/216 (28.7)	26/216 (12.0)	36/216 (16.7)
Anaemia (microcytic)	195/489 (39.9)	60/489 (12.3)	135/489 (27.6)
Change of bowel habit	118/385 (30.6)	43/385 (11.2)	75/385 (19.5)
Diarrhoea	104/322 (32.3)	23/322 (7.1)	81/322 (25.2)
Inflammatory bowel disease assessment	288/348 (82.8)	3/348 (0.9)	285/348 (81.9)
Clarification of barium enema findings	104/186 (55.9)	33/186 (17.7)	71/186 (38.2)
Rectal bleeding	306/605 (50.6)	71/605 (11.7)	335/605 (55.4)

Conclusion: Different indications for colonoscopy result in varying proportions of abnormal / normal procedures. Careful consideration of the indication for colonoscopy might help the endoscopy unit prioritise examinations when demand leads to long waiting times.

075 THE EPIDEMIOLOGY OF DISTAL HYPERPLASTIC POLYPS IN THE UK POPULATION

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Background: Hyperplastic polyps (HP) have always been considered unimportant lesions with no malignant potential. Consequently there has never been a proper description of their epidemiology in living subjects.

Aim: To accurately describe the prevalence, sex and age distribution of distal HPs in an asymptomatic UK population.

Method: 40,673 individuals aged 55 to 64 years had a flexible sigmoidoscopy (FS) as part of the UK FS screening trial. Subjects investigated with lower gastrointestinal endoscopy during the last two years, a history of inflammatory bowel disease, colorectal dysplasia or family histories of colorectal cancer were excluded. All polyps above the distal 5cm of the rectum smaller than 1cm diameter were recorded, removed and sent for histopathological assessment. Polyps 1cm or larger were removed at a later colonoscopy. Polyps in the distal rectum less than 3mm diameter were recorded but not included in the analysis of results.

Results: 19.1% of 20,518 males and 11.3% of 20,155 females had one or more histologically confirmed distal HPs (male: female ratio = 1.7:1; 95% ci 1.6–1.8; $p < 0.001$). 84.2% HPs were $\leq 4\text{mm}$ in diameter, 14.5% were 5–9mm and 1.2% ($n=129$) were $\geq 10\text{mm}$. The mean diameter was 3.4mm. The majority of distal HPs were located in the rectum (59.3%). 79.0% were sessile, 15.0% pedunculated and 2.3% flat or depressed. Males were more likely than females to have multiple distal hps (43.4% vs 34.2%; risk difference = 9.1%; 95% CI for risk difference 6.6–11.7%; $P < 0.001$). There were no sex differences in size, location or morphology. Neither prevalence, size, location or multiplicity changed with age in either sex.

Conclusion: Distal HPs are common. They occur more frequently and are more likely to be multiple in males than females. Most people have their full complement of distal HPs by 55 years.

076 FLAT COLORECTAL NEOPLASMS; THE INCIDENCE IN THE UK POPULATION

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Background: Flat and depressed colorectal adenomas/cancers have been described in the Japanese literature for almost 15 years, and more recently in the western population. The reported incidence in western countries, however, remains uncertain. One possible explanation for this is the endoscopic & histological definitions used.

Methods: To clarify the incidence and clinical importance of flat neoplasms in a Western population, 364 consecutive patients undergoing routine colonoscopy were assessed over a 6 month period (May–Oct 2000). All examinations were performed by two experienced Colonoscopists (BPS/NS) using standard Olympus video-colonoscopes. Dye spray was performed using 0.1% indigo carmine when suspicious areas were seen. Macroscopically Kudo's classification for flat adenomas was used and the histological diagnosis of dysplasia was based on the WHO system.

Results: Total colonoscopy (adjusted) was achieved in 95% of patients. Indications for colonoscopy were: bleeding (62), polyp surveillance (52), change in bowel habit (34) and others (216). In total 416 polyps were found in 170/364 patients with 9 cases of advanced cancer. Of these 25 were classified as flat (6%) and 391 polypoid (94%). 354/416 could be assessed histologically (21 flat; 336 polypoid). All flat lesions were neoplastic (adenomatous) while 39% of the polypoid lesions were non-neoplastic (inflammatory/hyperplastic). Of the neoplastic lesions severe dysplasia was found in 3% of the polypoid lesions and in 50% of flat& depressed lesions.

Abstract 76, Table 1

	Mild/mod.	Severe/Dukes A	(Non-neoplasia)
Polypoid	97%(195/202)	3%(7/202)	134
Flat elevated	100%(17/17)	0	0
Flat & depressed	50%(2/4)	50%(2/4)	0

Conclusion: In this study the macroscopic incidence of flat adenomas during the procedure was 6% and the incidence to the all adenomatous lesions was 9.4%. According to our result, flat elevated lesions may have the similar characteristics as polypoid lesions in terms of malignancy. On the other hand, as flat and depressed lesions had a high incidence of malignancy, Colonoscopists should be more meticulous in detecting especially flat and depressed lesions.

077 FAMILIAL COLORECTAL CANCER; OUTCOME OF COLONOSCOPIC SURVEILLANCE IN DOMINANT FAMILIES WITH AND WITHOUT HEREDITARY NONPOLYPOID COLORECTAL CANCER MICROSATELLITE INSTABILITY

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Introduction: Hereditary nonpolyposis colorectal cancer (HNPCC) is an important dominantly inherited predisposition to colorectal cancer (CRC). It is caused by mutations in DNA mismatch repair genes, which are characterised by microsatellite instability (MSI) in tumours. It has been proposed that there are other important genetic predispositions to CRC.

Aims: Assess the outcome of colonoscopic surveillance in dominant CRC families stratified according to their MSI status

Methods: Individuals with a family history of CRC are stratified according to their empirical lifetime risk of developing CRC and offered colonoscopic surveillance if the risk is ≥ 1 in 10. 27 CRC dominant pedigree families (at least 3 individuals affected over 2 generations, 1 a direct relative of the other 2) were stratified according to the presence (n=11) or absence (n=16) of the HNPCC MSI phenotype (MSI-H) in the tumour of 1 affected family member. The results of colonoscopic surveillance in at-risk family members were compared.

Results: MSI-H was observed in 11/27 families (40%). The median age at first colonoscopy on family members was 35 years. Adenomas were observed in 30% of colonoscopies overall. Advanced polyps or cancer was observed in 15% of colonoscopies regardless of MSI status (MSI-H + 5/33, MSI- 6/39). The only variable predictive of finding a polyp was age.

Conclusions: More than 50% of the CRC risk in autosomal dominant pedigrees may be due to non-HNPCC genetic predispositions. These individuals are at increased risk for CRC and should undergo colonoscopic surveillance. The genetic basis for these non-HNPCC predispositions remain to be elucidated.

078 IN VIVO GENE THERAPY FOR COLON CANCER USING ADENOVIRUS-MEDIATED TRANSFER OF CYTOSINE DEAMINASE/URACIL PHOSPHORIBOSYLTRANSFERASE, AND 5-FLUOROCYTOSINE

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Background: Gene therapy is a novel treatment modality for colon cancer. Virus-directed enzyme prodrug therapy involves the transfer of a therapeutic enzyme, which converts a non-toxic prodrug into a cytotoxic metabolite, which is localised to the tumour surroundings and thus minimizes systemic side effects.

Methods and results: A replication-deficient adenovirus vector was constructed, which encoded the bacterial enzyme, cytosine deaminase (CD), under the control of the strong cytomegalovirus promoter (Ad.CMV.CD). Cytosine deaminase converts the antifungal agent, 5-fluorocytosine (5-FC), into 5-fluorouracil (5FU), one of the most active chemotherapy agents in colon cancer. *In vitro*, human colon cancer cell lines infected with Ad.CMV.CD are sensitised to the prodrug 5-FC. Moreover, cloning the bifunctional fusion gene, cytosine deaminase:uracil phosphoribosyltransferase (CD:UPRT), into the virus (Ad.CMV.CD:UPRT), increases virus potency by 100-fold. UPRT enhances the conversion of the 5-FU generated into its active metabolite. Cells infected with Ad.CMV.CD:UPRT are markedly sensitised to either 5-FC or 5-FU. This may enable a VDEPT approach to use 5-FC, or potentially lower doses of 5-FU in order to minimise systemic toxicity and maximise anti-tumour effects. Additionally, there is a strong bystander effect, where surrounding cells not infected with virus are also sensitised to prodrug. *In vitro*, the majority of tumour cells can be killed by prodrug when only 10% of cells are infected with virus. *In vivo*, treating mice with established colon cancer xenografts with intratumoural injections of Ad.CMV.CD:UPRT and intraperitoneal 5-FC, significantly reduced tumour growth compared to controls ($p = 0.03$, Mann-Whitney U test).

Conclusion: Adenovirus-mediated, enzyme prodrug therapy for colon cancer with the fusion gene, CD:UPRT and the prodrug 5-FC, is promising in these preclinical studies and warrant further evaluation.

079 DOES LAPAROSCOPIC CHOLECYSTECTOMY WITHOUT INTRAOPERATIVE CHOLANGIOGRAPHY LEAD TO A HIGH INCIDENCE OF RESIDUAL STONES?

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Background: The need for intraoperative cholangiography to identify asymptomatic common bile duct (CBD) stones in patients undergoing laparoscopic cholecystectomy (LC) is controversial.

Aim: The aim of this study was to test the validity of the assumption that LC without intraoperative cholangiogram results in a high incidence of residual CBD stones.

Methods: Between January 1997 and July 2000, 456 patients underwent cholecystectomy, of which 422 had LC. A policy of selective preoperative ERCP was adopted using standard clinical, biochemical and ultrasonographic criteria. Postoperative ERCP was performed for pain, jaundice, abnormal biochemistry or a finding of dilated cystic duct at operation.

Results: Preoperative ERCP was performed in 23.2%(106) of all operations and 21.5% of LCs (91/422). CBD stones were detected in 30(28%). Preoperative ERCP achieved a 96.6% duct clearance rate, a 100% positive predictive value and a 97% negative predictive value. Residual stones following LC were detected in 1.18% (5/422). Postoperative ERCP was performed in 4 of the 91 patients who had preoperative ERCP with detection of 1 residual stone (1.09%). 22 of 331 patients who did not have preoperative ERCP, required investigation with ERCP or MRCP with detection of 4 residual stones (1.20%). Overall duct clearance rate by ERCP was 94%(32/34). There were no major complications from ERCP.

Conclusion: LC without intraoperative cholangiogram coupled with a policy of selective preoperative ERCP resulted in a residual stone rate similar to other management options. ERCP has a major role in therapy but its diagnostic role may diminish with increasing use of non-invasive MRCP.

080 INTRACELLULAR pH OF THE BRAIN IN CHRONIC HEPATIC ENCEPHALOPATHY (HE): A ^{31}P MR SPECTROSCOPY (MRS) STUDY

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Aim: To determine the brain intracellular pH (pHi) in patients with chronic HE non-invasively, using *in vivo* ^{31}P MRS.

Patients: 82 patients (46 M; 36 F), with biopsy-proven cirrhosis of mean (range) age 52 (31-77) yr and 30 aged-matched controls were

studied. 11 subjects had no evidence of neuropsychiatric impairment, 37 had evidence of minimal HE and 34 had overt HE.

Methods: Unlocalised spectra were acquired from the entire head in 48 patients (TR 5s; 64 averages). Spectra from the basal ganglia (BG) were acquired in 34 patients, using a 3-D CSI technique (TR 5s; 2048 averages). pH_i values were calculated from the chemical shift difference between the inorganic phosphate (P_i) and phosphocreatine (PCr) resonances. The % P_i, PCr and βNTP signals relative to the total ³¹P signal and peak area ratios of P_i and PCr relative to βNTP were also measured.

Results: There were no pH_i differences between patients and volunteers in ³¹P MR spectra from the whole head or BG. There was no correlation between pH_i and the severity of HE or Child score. There was no change in spectra from the whole head, but in BG spectra, there was a significant increase in mean P_i/NTP (p=0.02) and PCr/NTP (p=0.009). The mean %P_i and %PCr were also increased (p=0.06; p=0.05). When the patients were classified according to the severity of HE, those with overt disease had a higher mean P_i/NTP and %P_i (p=0.03; p=0.01), compared to controls.

Conclusion: Our results suggest that there are detectable bioenergetic abnormalities in patients with minimal and overt HE and that any pH change, related to mitochondrial dysfunction, is probably a secondary, rather than a primary phenomenon.

081 HEMODYNAMIC CONSEQUENCES OF PRECONDITIONING IN LIVER ISCHAEMIA-REPERFUSION INJURY

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Background: Ischaemic preconditioning (IPC) may increase tolerance of the liver to ischaemic insults of surgery. IPC may be mediated via nitric oxide (NO). The hemodynamic changes of IPC have not been correlated to NO metabolism.

Material and Methods: Sprague Dawley rats were subjected to 45 mins lobar ischaemia followed by 2 hr reperfusion (IR). L-arginine or L-NAME were administered to stimulate or block NO synthesis. Study groups (n=6) had, (1) sham laparotomy, (2) IR, (3) IPC with 5 min ischaemia and 10 min reperfusion before IR, (4) L-arginine before IR, (5) L-NAME + IPC before IR. Hepatic tissue oxygenation was measured by near infrared spectroscopy (NIRS) and hepatic microcirculation (HM) by laser doppler flowmeter (LDF). Liver function tests and nitrates were analysed. Differences between groups and confidence intervals were established using analysis of variance (ANOVA) with Bonferroni test, and paired student's t test.

Results: IR injury produced significant reduction in HM (31.6% of preischaemic value, p=0.00 vs baseline). IPC improved the HM (49.5%, p<0.02 vs controls) upon reperfusion. IPC improved hepatic oxyhemoglobin and cytochrome oxidase (both p<0.05 vs controls). NO stimulation and blockade did not influence HM or hepatic tissue oxygenation. IPC as well as L-arginine treatment significantly increased nitrates and decreased liver enzymes. L-NAME administration with IPC prevented the rise in nitrates and decrease in liver enzymes.

Conclusion: IPC resulted in improvement of HM and hepatic tissue oxygenation following IR, but the effect may not be solely mediated by nitric oxide.

Oesophagus Posters: 082-111

082 REPEAT OESOPHAGEAL AMBULATORY pH MONITORING—IS IT WORTHWHILE? A RETROSPECTIVE ANALYSIS OF 6000 PATIENTS

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Introduction: Patients who have undergone oesophageal pH studies are re-referred for a variety of reasons, after varying time intervals. The aim was to determine if repeating the pH study was likely to alter the diagnosis.

Patients and methods: Data was reviewed from adult patients who were studied between January 1985 and June 2000. Over 6000 patients have had pH tests, of which there were 211 patients with two or more studies. As therapeutic interventions potentially alter the underlying pathology, only the 111 patients who had no therapy at any stage were included. Both initial and repeat referrals and subsequent diagnoses, were stratified and analysed. The total percentage of reflux (pH<4) time (TPR) and DeMeester score were examined. The initial TPR was also compared to the repeat studies.

Results: Patients diagnosed initially as normal (TPR<5.78 or DeMeester score<14.7) were unlikely (p<0.05) to have their diagnosis changed if their DeMeester score was less than 5.8 (average score 2.0 with SD 1.9). Non-intuitively, the TPR could not predict (p<0.05) whether an initial diagnosis of normal would change. In those initially diagnosed with gastro-oesophageal reflux disease (GORD), TPR and DeMeester score were not predictive (p<0.05). There was a poor correlation between the initial and repeat TPR, even in those whose initial diagnosis was confirmed by the second test (correlation coefficient R²=0.008). There was no consistency of TPR either, in specific groups where throughout the diagnosis was GORD (R²=0.016) or where throughout the diagnosis was normal (R²=0.025).

Conclusion: There is a high degree of intra-patient variation in TPR, in interval repeated studies. In those initially diagnosed as normal, surprisingly TPR is not predictive however a DeMeester score below 5.8 is a relative contra-indication to performing a repeat pH study.

083 THREE-HR POSTPRANDIAL pH MONITORING IS USEFUL IN EXCLUDING GASTRO-OESOPHAGEAL REFLUX DISEASE IN SYMPTOMATIC PATIENTS

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Introduction: Currently ambulatory 24hr oesophageal pH monitoring is the gold standard for the diagnosis of gastro-oesophageal reflux disease. This long period of oesophageal intubation is unpleasant. Thus the aim of this study was to determine if a 3hr postprandial study would be as sensitive as the 24hr study.

Patients and methods: Two hundred symptomatic patients (86 male, 114 female, average age 56yrs 3 months) were studied. A 3hr postprandial period was analysed and compared to a standard ambulatory 24hr oesophageal pH monitoring (Synectics Medical). A positive test was defined as >5.78% of the total period of pH<4. The De Meester score was also calculated from the 24hr study, with a score >14.72 regarded as positive.

Results: The 3hr post prandial oesophageal pH correlated well with the 24hr study (r=0.885, p<0.001), and the De Meester score (r=0.82, p<0.001). When only supine periods during the 3hr test was examined this again correlated well with the complete 24hr study (r=0.884, p<0.001), and the De Meester score (r=0.796, p<0.001). The negative predictive value of the 3hr study was 92% when compared with the 24hr test, and 88% when compared with the De Meester score.

Abstract 83, Table 1

	3hr pH vs 24hr pH	3hr pH vs De Meester score
Negative predictive value	92%	88%
Positive Predictive value	65%	80%
Sensitivity	88%	85%
Specificity	75%	82%

Conclusions: The 3hr post prandial study is a sensitive test for the detection of gastro-oesophageal reflux disease, and a negative 3hr test is useful in excluding disease in symptomatic patients.

084 CLINICAL ROLE OF OESOPHAGEAL MANOMETRY

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Background: Although several modalities are available to investigate oesophageal motility disorders, most gastroenterologists regard manometry as the gold standard. Manometry is increasingly available in district general hospitals but the clinical utility of the investigation in this setting remains unclear.