

Stomach and duodenum TU1-TU6

TU1

USE OF SELF-EXPANDABLE STENTS IN THE TREATMENT OF BENIGN PEPTIC OESOPHAGEAL STRICTURES IN THE ELDERLY.

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The use of self-expandable stents in the management of malignant oesophageal strictures has become well established. The majority of benign peptic oesophageal strictures can be successfully managed using endoscopic or fluoroscopically guided balloon oesophageal dilatation combined with long term drug therapy, particularly using Proton pump inhibitors. Although endoscopic oesophageal dilatation can be performed on an outpatient basis it requires repeated hospital visits. There is a small risk of oesophageal perforation whilst cardio-respiratory complications may be encountered during the use of intravenous sedation in elderly patients. Self-expandable Strecker oesophageal stents (Boston Scientific Corporation, Boston) were used in three elderly female patients aged 91, 98 and 100 years respectively. All patients had previously required repeated endoscopic oesophageal dilatations over a 5 year period despite the use of long term Omeprazole therapy. Self-expandable stents were inserted in all patients under mild sedation following preliminary stricture dilatation. All patients have obtained excellent relief of symptoms following stent insertion and have now been followed up for approximately 12 months. They are able to swallow normally and have continued on long term maintenance Omeprazole therapy. There is a theoretical risk of developing an additional peptic stricture above the stent but this is unlikely to be a significant problem in these patients with the use of long term Omeprazole therapy and their likely life expectancy.

TU3

THE EFFECTS OF Na METHYLHISTAMINE ON GASTRIC ACID SECRETION IN HUMAN VOLUNTEERS

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Background: *Helicobacter pylori* (Hp) produces Na Methyl Histamine. (NaMH). The effects of this substance on the physiology of the human stomach is unknown. NaMH is an agonist of both H2 and H3 receptors. Its histamine H3-agonist effect is expected to inhibit enterochromaffin-like cells which might decrease acid secretion. However we find that it stimulates rabbit parietal cells via histamine H2-receptors, and also releases gastrin from rabbit G-cells. Therefore we investigated the overall effect of luminal NaMH on acid secretion and gastrin release in human volunteers.

Methods: Volunteers fasted overnight. Terfenadine, 120mg, was given 1 hour before the study to block histamine H1-receptor effects. A naso-gastric tube was passed and connected to an automated syringe device to ensure adequate mixing of the gastric contents. Gastric acid output was measured by continuous intra-gastric titration of a 5.8% glucose solution to pH 5.0. The intragastric solution was changed every 30 min. NaMH was added at 10^{-4} M, 10^{-5} M, and 10^{-6} M, with basal periods before each dose. Blood was collected for gastrin assay. Hp status was determined by 14 C Urea breath test.

Results: Eleven volunteers took part; 5 female and 6 male. Four were infected with Hp. In the Hp negative group NaMH stimulated acid output from a basal value of 3.8 ± 1.3 (mmol/h mean + SEM), to 5.2 ± 2.1 at 10^{-6} M (NSD) and 6.0 ± 1.7 at 10^{-5} M ($P < 0.05$ vs. basal). NaMH 10^{-4} M produced no further rise. By way of contrast, initial results in the Hp positive group showed a higher basal acid output; 7.5 ± 2.7 ($P < 0.05$ vs. uninfected) and no response to NaMH; 5.1 ± 1.9 at 10^{-5} M. Fasting plasma gastrin concentrations were 7.5 ± 1.5 pmol/l in uninfected subjects compared to 30.5 ± 7.9 pmol/l in infected subjects ($P < 0.05$). NaMH had no significant effect on plasma gastrin levels. **Conclusion:** The *H. pylori* product NaMH stimulated acid secretion in Hp negative subjects when infused into the gastric lumen. No effect was seen on gastrin release. By contrast Hp positive patients had higher basal acid output and did not respond to NaMH. Thus NaMH may contribute to the elevated basal acid output seen in *H. pylori* infection.

TU2

DEGREE OF SUPPRESSION OF GASTRIC ACID SECRETION BY OMEPRAZOLE IS RELATED TO *H. PYLORI* STATUS. D. Gillen, A. Wirz, K.E.L. McColl. University Dept. of Medicine & Therapeutics, Western Infirmary, Glasgow, U.K.

Introduction: Proton pump inhibitors (PPIs) are very commonly used drugs. Recent data indicate that they cause more marked elevation of intragastric pH in *H. P.*-infected individuals. It is not clear whether this is due to a neutralising effect of ammonia produced by *H. pylori* urease or to a more marked inhibition of acid secretion.

Aim: To assess the effect of *H. pylori* status on acid secretion during PPI therapy.

Subjects and Methods: 18 *H.P.*-ve and 10 *H.P.*+ve healthy volunteers were studied. *H. pylori* status was confirmed by the 14 C-urea breath test. Prior to commencing the PPI therapy, basal acid output, acid output to gastrin releasing peptide (40pmol/kg/h) (GRP) and maximal acid output to Gastrin-17 (MAO) were measured on separate days. Omeprazole 40mg/day was then taken in the morning daily for eight weeks. On separate mornings in the last two weeks of this course, the acid secretion studies were repeated (24 hours after the last dose).

Results:	<i>H.P.</i> negative			<i>H.P.</i> positive		
	Pre- Omepr.	On Omepr.	% Inhib.	Pre- Omepr.	On Omepr.	% Inhib.
Basal intragastric pH	1.61	3.74*		1.50	8.04	
Basal acid output (mmol/h)	3.4	0.3*	82%	3.2	0.0	100%
GRP acid output (mmol/h)	9.6	3.8*	64%	14.2	0.0	100%
MAO _{G17} (mmol/h)	36.0	18.2*	52%	34.6	7.1	80%

Values are medians. *Indicates difference from *H.P.*+ve at $p < 0.05$.

Discussion and Conclusions: This study indicates that the inhibition of gastric acid secretion produced by PPI therapy is much more profound in *H.P.*+ve individuals. The magnitude of this effect cannot be explained by the neutralising effect of bacterial ammonia. It may be explained by the body gastritis which develops in *H.P.*+ve subjects during PPI therapy impairing acid secretory function and thus augmenting the effect of the drug. This profound suppression of acid secretion may have deleterious effects by facilitating gastric bacterial colonisation and consequently predisposing to gastric carcinoma. Eradication of *H. pylori* may be appropriate prior to long-term PPI therapy, but this may reduce the efficacy of PPI therapy in reflux disease.

TU4

NEW, INTERNATIONALLY APPLICABLE, POLYMERASE CHAIN REACTION-BASED TYPING OF *Helicobacter pylori vacA*. JC Atherton, RJ Twells, CJ Hawkey, RM Peek Jr. *, TL Cover*, MJ Blaser*. Div. Gastroenterology and Institute of Infections and Immunity, University of Nottingham, Nottingham NG7 2UH, *Div. Infectious Diseases, Vanderbilt University and VAMC, Nashville, USA.

Typing *H. pylori vacA* is important because, in the US, *vacA* structure has been associated with gastric epithelial damage and ulceration. A previous PCR-based typing system successfully classified all U.S. strains tested, but failed to classify *vacA* mid-regions of Japanese and various other strains. We sought to investigate the extent of *vacA* mid-region diversity between US strains and strains from other countries, and to devise an internationally applicable typing system.

Methods and Results: We studied 78 *H. pylori* isolates of which 13/13 Japanese, 2/6 Chinese, 3/9 Thai, 1/8 Peruvian and 0/42 US isolates had *vacA* mid-regions we could not previously classify. We PCR-amplified, cloned and sequenced, extended (1.7Kb) *vacA* mid-regions of 1-2 untypeable strains from each country. All proved to be type m1 variants except one Chinese strain which was m1 proximally and m2 distally with a clear crossover site. Annealing sites for the unsuccessful m1 primers had up to 3/19 and 7/20 non-complementary bases. *vacA* sequence comparisons using these strains, m2 strains from the same populations, and other published strains, showed that diversity was greater among m1 strains (1-12% nucleotide differences over 294bp) than m2 (0-6%), but that differences were most marked between m1 and m2 strains (22-27%). Next, we devised two new PCR-based typing strategies. The first used conserved primers spanning a 75bp imperfect repeat found only in m2 strains, and differentiated products by size. The second used four primers in a single reaction: two new m1 primers and two previously described m2 primers. We applied both strategies to all 78 isolates. Results agreed entirely with previous *vacA* typing, except that for both strategies all previously untypeable strains were m1. As expected, the Chinese m1/m2 strain appeared m1 by strategy 1 and gave a uniquely sized product (of the predicted size) using strategy 2.

Conclusions: Despite variability in the *vacA* mid-region, all strains can be typed as m1 or m2. Finding an intermediate m1/m2 type implies *in vivo* recombination between strains. This typing system will aid studies linking *vacA* genotype with disease in countries other than the US.

TUS

VIRULENT *HELICOBACTER PYLORI* (HP) IN PATIENTS WITH GASTRIC AND OESOPHAGEAL ADENOCARCINOMA.

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Introduction: Gastric carcinogenesis can be explained by a model based on HP-mediated inflammation facilitating progression from gastritis to atrophy, dysplasia and cancer. Mucosal inflammation which occurs when HP colonises the stomach is more severe when the strains express CagA and VacA. If HP-mediated inflammation is the main pathogenetic factor in gastric carcinogenesis, then virulent proinflammatory strains of HP should be over represented among patients with gastric cancer when compared to other disease groups in which HP inflammation is not a factor.

Method: In an unselected series of patients with gastric (GA) or oesophageal (OA) adenocarcinoma, HP status was determined by serology/¹³C-UBT/CLO-test/histology. CagA and VacA status of the colonising HP was determined indirectly by detecting antibodies to these proteins in patients sera by an immunoblot assay. Using a novel virulence scoring system, a putative HP virulence load was assigned to each patient depending on whether they were colonised by HP and whether the HP strain they harboured expressed either CagA or VacA or both virulence factors. Virulence load increased in a stepwise fashion: - patients scored 0 if HP-ve, 1 if HP+ve and -ve for CagA and VacA, 2 if HP+ve and also +ve for either CagA or VacA and 3 if HP+ve and also +ve for CagA and VacA.

Results: GA (n=26) OA (n=26), median age were 74 and 67 respectively. In the GA group 21/26 patients were HP+ve and 19/21 harboured strains which were +ve for CagA or/and VacA. In the OA group 14/26 were HP+ve and only 7/14 harboured strains +ve for CagA or/and VacA. When our virulence scoring system was used to assign virulence/inflammatory load, patients with GA scored a median of 2 (range 0-3) compared with OA patients who scored 1 (range 0-3), p=0.0016 Mann-Whitney U Test.

Conclusion: Compared to an OA control group, the majority of patients with GA are colonised by virulent pro-inflammatory strains of HP. This study supports the HP inflammatory model for gastric carcinogenesis. An alternative interpretation could be that colonisation by virulent HP protects against oesophageal adenocarcinoma.

TU6

THE PROLIFERATIVE STATUS OF ENTEROCHROMAFFIN-LIKE (ECL) CELLS IN THE GASTRIC MUCOSA; THE PLOT THICKENS

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There has been considerable interest in ECL cell hyperplasia, in recent years, mainly because of concern that powerful antisecretory therapy may lead to the development of ECL cell carcinoids. The mechanism of development of ECL cell hyperplasia in chronic atrophic gastritis, whether or not the patient is on antisecretory therapy, has been assumed to be due to proliferation of the ECL cells themselves; this is because of findings in experimental animals that indicate that the ECL cell lineage is a self-renewing population. There is little or no direct experimental evidence, however, on the proliferative status of this important lineage in the human stomach.

Consequently, we have examined the fundic gastric mucosa of normal humans, patients on long-term antisecretory therapy, and patients with atrophic gastritis showing diffuse, linear and micronodular hyperplasia, and with ECL cell carcinoids. In addition, we evaluated fundic mucosa from *Mastomys*, an important animal model for ECL cell hyperplasia and neoplasia: control animals, animals with ECL cell hyperplasia and ECL cell carcinoids induced by loxitidine were available. All tissues were double-immunostained using chromogranin A as an endocrine cell marker, and PCNA and MIB-1 as proliferative markers.

We were unable to demonstrate double-labelled cells in normal human corpus or in patients with diffuse, linear or micronodular hyperplasia, despite counting in excess of 20,000 chromogranin A positive cells in each group. However, ECL cell carcinoids in humans contain numbers of double-labelled cells (up to 0.15%). However, *Mastomys* corpus contains proliferative ECL cells, as previously reported, and we demonstrated that up to 3% of chromogranin positive cells were double-stained in ECL cell hyperplasia, and 4% in ECL cell carcinoids.

We conclude that (i) as assessed by chromogranin A, neither normal nor hyperplastic ECL cells in the human stomach appear to have proliferative potential; (ii) *Mastomys* ECL cells form a renewing population and undergo hyperplasia after loxitidine-induction which involves cell division, which may reflect different rates of cell turnover in each species. These findings indicate (a) that the mechanism of ECL cell hyperplasia in the human stomach does not involve proliferation of ECL cells themselves, although neoplastic ECL cells themselves can divide, and (b) that lineage relationships in the human and animal stomach differ. The *Mastomys* model thus appears appropriate for studies of ECL cell proliferation.

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W7

VALUE OF THE HELISAL TEST IN SCREENING DYSEPTIC PATIENTS FOR *H. PYLORI* INFECTION - A. Sinha, C. Treharne, L. Murray, D.W. Williams, M.J. Dew, Prince Philip Hospital, Llanelli.

Introduction: *H. Pylori* antibody seropositivity as determined by laboratory based ELISA tests or ELISA kits has been proposed as a screening test for *H. Pylori* infection in dyspeptic patients without sinister symptoms, especially those below 45 years, with diagnostic endoscopy offered to only the seropositive group. The Helisal test (Cortecs diagnostics), which is one such Rapid Whole Blood Test, is increasingly being used in general practice for this purpose. This study assesses the reliability of this approach.

Aim: To assess the value of the Helisal test in screening dyspeptic patients for *H. Pylori* infection.

Methods: 207 consecutive patients (102 male, 105 female) referred for Open Access endoscopy were tested immediately before endoscopy. Serum samples were obtained for a reference laboratory based ELISA test for *H. Pylori* antibodies. Infection was confirmed if CLO test at 24 hours and microscopic visualisation of the organism on biopsy were both positive, and excluded if both were negative.

Results: *H. Pylori* infection found in 69/187 (36.9%) patients [Age < 45 - 13/39 (33.3%); Age >= 45 - 56/138 (40.58%)]. The Helisal test had a sensitivity of 0.84, but a specificity of only 0.46 [Positive predictive value (PPV) 0.43, Negative predictive value (NPV) 0.75, False positive rate (FPR) 0.54, False negative rate (FNR) 0.16, Likelihood ratio (LR) 1.56]. The laboratory ELISA test had a sensitivity 0.84, but the specificity was 0.79 [PPV 0.62 NPV 0.82, FPR 0.21, FNR 0.16, LR 4]. Correlation of Helisal test with Laboratory based ELISA test was poor. Both tests performed similarly in the <45 group and the >45 group.

Conclusion: Of the 122 patients that had a positive Helisal test in this study, 64 (52.46%) were falsely positive. Reliance on a negative Helisal result to restrict endoscopy would have resulted in 16% (11/69) cases of *H. Pylori* infection being missed. The poor performance of this test makes it unsuitable for use in screening for *H. Pylori* infection.

W8

One year follow-up of a randomised trial of pre endoscopy screening for *H. pylori* in the management of dyspepsia.

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Background: The safety and savings in endoscopy derived from not endoscoping *H. pylori* seronegative dyspeptic patients has been demonstrated in short term studies of six month duration. The long term outcome of such a management strategy is not clear what. We report the final 12 month follow-up in a prospective randomised trial, for which we reported interim results of this study has already been presented to the society. **Design:** 417 patients under the age of 45 years referred to a direct access endoscopy service were screened with a validated questionnaire and *H. pylori* serology (*Helico-G* ELISA). A cut off level of 6.3u/ml had been previously determined to be suitable for screening. 154 patients (56% male) had serology titres below 6.3u/ml and were randomised to have either endoscopy or no endoscopy. All patients were returned to their GPs for further management. Patients with a history of weight loss of more than 1/2 stone in 6 months, dysphagia, anaemia or persistent vomiting or on regular NSAIDs were excluded. Six and twelve month assessment was carried out by postal questionnaire.

Results: 120/154 (79%) and 82/154 (53%) questionnaires were returned at 6 and 12 months respectively. Table shows results at 12 months expressed as medians.

	Endoscopy (43)	No Endoscopy (39)	P
Symptom score	1	1	NS
Disability score	0	1	NS
Days off work	0	0	NS
GP visit	0	0	NS
Prescriptions score	0	1	NS
Self medications score	0	1	0.05
Specialist referral	6/38 (16%)	13/34 (38%)	0.06
Endoscopy referral (n)		6/39 (15%)	

Summary: There were no significant differences in symptoms, disability, GP visits and prescriptions between the two groups. 46% (6/13) of the non endoscoped group referred for specialist consultations were endoscoped. At one year 85% of endoscopies were saved.

Conclusions: It is safe and more cost effective in the long term to manage young *H. pylori* negative dyspeptic patients without endoscopy.

W9

MARKED REBOUND ACID HYPERSECRETION FOLLOWING OMEPRAZOLE THERAPY IN *H. PYLORI* NEGATIVE SUBJECTS. D. Gillen, A. Wirz, K.E.L. McColl. Univ. Dept. of Medicine & Therapeutics, Western Infirmary, Glasgow, U.K.

Introduction: Rebound hypersecretion of gastric acid is a well established class effect of H_2 -antagonists. Previous studies have suggested that this phenomenon does not occur with proton pump inhibitors (PPIs). However, the effect may have been masked by PPI induced *H. pylori* body gastritis.

Aims: To establish whether rebound acid hypersecretion occurs with PPIs when subjects are stratified by *H. pylori* (*H.P.*) status.

Subjects and Methods: 11 *H.P.*-ve and 7 *H.P.*+ve healthy volunteers were examined. Their *H.P.* status was determined by the ^{14}C -urea breath test. Their basal acid output (BAO) and G17 stimulated maximal acid output (MAOG17) and maximal acid output in response to gastrin releasing peptide (MAOGRP) were measured before and 2 weeks after completing a 2 month course of omeprazole 40mg/day.

Results and Discussion:

	<i>H.P.</i> negative			<i>H.P.</i> positive		
	Pre-omep. (n=11)	Post-omep. (n=11)	% change	Pre-omep. (n=7)	Post-omep. (n=7)	% change
BAO (mmol/h)	4.6	7.5*	+63.0%	4.9	4.8	-2.0%
MAOG17 (mmol/h)	31.6	41.2*	+30.4%	32.5	39.3	+21%
MAOGRP (mmol/h)	9.8	15.5*	+58.2%	15.2	12.1	-20%

All values are means. *Indicates significantly higher than pre-omep. at $p < 0.01$.

In the *H.P.*-ve subjects there was marked rebound hypersecretion of acid following omeprazole therapy apparent with each of the 3 acid secretion tests. There was no rebound hypersecretion of acid in the *H.P.*+ve subjects and this may be due to the body gastritis occurring in *H.P.*+ve subjects during omeprazole therapy impairing gastric acid secretion and thus masking the rebound phenomenon.

Conclusion: There is marked rebound hypersecretion of gastric acid following PPI therapy in *H. pylori*-negative, but not *H. pylori*-positive subjects.

W11

RANITIDINE TREATMENT INDUCES DYSPEPSIA IN PREVIOUSLY ASYMPTOMATIC HEALTHY VOLUNTEERS. A. Smith, D. Gillen, K. Cochran, E. El-Omar, K.E.L. McColl. University Dept. of Medicine & Therapeutics, Western Infirmary & Victoria Infirmary, Glasgow, Scotland.

Background: Dyspeptic symptoms frequently rapidly recur following cessation of H_2 receptor antagonist therapy. We have previously shown that in *H. pylori*+ve healthy volunteers basal and gastrin releasing peptide (GRP) stimulated acid secretion are increased by 96% and 56% respectively 3 days after completing a two month course of ranitidine 300mg nocte compared to pre-treatment values (Am. J. Gastroenterol., 1996; 91: 355-359). It is unknown whether this rebound acid hypersecretion causes dyspeptic symptoms.

Aim: To determine whether cessation of H_2 antagonist treatment results in the *de novo* development and/or aggravation of dyspepsia.

Subjects and Methods: Thirty *H. pylori* positive healthy volunteers were randomised in a double blind fashion to receive either ranitidine 300mg nocte or placebo tablets for two months. All subjects had *H. pylori* infection confirmed using serology and ^{13}C -urea breath test. The two groups were matched for age, sex, body weight, smoking and alcohol consumption. Dyspeptic symptoms were measured using a validated questionnaire. Symptoms were scored for one week prior to entry into the study and for the 10 days following cessation of the treatment.

Results: Compliance was similar in the two groups (active 95%, placebo 98%, $p=NS$). The mean dyspepsia score before treatment was 0.86 in the active group and 0.53 in the placebo group ($p=NS$). The mean dyspepsia score for the 10 days after stopping treatment was 5.4 (range 0-30) in the active group and 0.93 (range: 0-9) in the placebo group ($p < 0.03$). 53% experienced dyspepsia in the 10 day period following active therapy versus 13% following placebo.

Conclusions: These results indicate that a two month course of ranitidine 300mg nocte is followed by the development of new dyspeptic symptoms in *H. pylori* positive healthy volunteers. This finding indicates that rebound acid hypersecretion following withdrawal of H_2 antagonist therapy is of clinical significance. It is now important to determine whether the dyspepsia is due to the rebound acid hypersecretion causing acute peptic ulceration.

W10

REFLUX SYMPTOMS IN THE LONG TERM FOLLOW UP OF PATIENTS AFTER *HELICOBACTER PYLORI* ERADICATION AE Griffiths, MR Thursz, D Pryce, MM Walker. Departments of Gastroenterology and Histopathology, Imperial College School of Medicine at St Mary's, Norfolk Place, London W2.

Background Symptomatic relapse after *H. pylori* (*Hp*) eradication in duodenal ulcer (DU) patients is common and is only rarely due to proven ulcer recurrence. Recent reports suggest that eradication of *Hp* is associated with the onset of gastro-oesophageal reflux disease (GORD) one to two years later.

Methods A questionnaire was sent to 85 individuals who had completed a similar questionnaire 2 years previously, just prior to *Hp* eradication. This included questions about symptomatology, medication, weight and smoking and alcohol history. Eradication was confirmed by ^{13}C urea breath test at follow up.

Results 45 patients returned the questionnaire (53% response). 32 were from patients known to have cleared *Hp*; 20 of these had DU originally, 19 were male and median age was 55 (range 25-79). The remaining 13 replies were from patients who had not cleared *Hp* (5 patients) or in whom a breath test result was unavailable (8 patients); 3 had DU, 5 were male and median age was 57 (range 32-82). In the *Hp* eradicated group with DU 9/20 (45%) had heartburn/reflux symptoms at 2 years follow up. However 17 (85%) had these symptoms prior to treatment. In the non-DU, *Hp* eradicated patients the figures were similar with 75% having heartburn pre-treatment and 42% at 2 years. In the non-eradicated group the corresponding frequencies of heartburn were 54% initially and 38% at 2 years. No individual in any group developed heartburn/reflux symptoms during 2 years of follow up. Other findings were that 65% of 32 successfully treated patients remained symptomatic at follow up, with 53% still requiring medication, chiefly antacids. 9% stated that their symptoms are worse now than they were before treatment. Changes in weight or in alcohol consumption had no bearing on current symptoms though increased cigarette smoking was associated with fewer symptoms.

Conclusions Contrary to previous reports we have found no evidence of new symptoms of GORD in the long-term follow up of patients undergoing *Hp* eradication for DU or for other *Hp* related conditions.

W12

REGULATION OF CORPUS MUCOSAL FUNCTION IN *H.P.* INFECTED DU PATIENTS VERSUS HEALTHY VOLUNTEERS. D. Gillen, E. El-Omar, A. Wirz, J.E.S. Ardill, K.E.L. McColl. Univ. Dept. of Medicine & Therapeutics, Western Infirmary, Glasgow, U.K.

Introduction: We have demonstrated a two-fold greater acid response to gastrin in DU patients compared to *H.P.*+ve healthy volunteers (*H.V.*).

Aim: To determine whether the increased acid response in DU patients is due to difference in (1) parietal cell mass (PCM), (2) sensitivity to gastrin, (3) inhibitory control or (4) combination of these.

Subjects and Methods: 34 *H.P.*-ve HVs, 19 *H.P.*+ve HVs and 18 *H.P.*+ve DU patients were examined. On separate mornings, after a 30 minute basal acid collection, either 7, 20, 60, 180 and 800pmolKg⁻¹h⁻¹ of Gastrin17 or 7, 20, 60 and 120pmolKg⁻¹h⁻¹ of CCK8 were infused intravenously over 30 minute periods with corresponding acid collections. Plasma for gastrin estimation was collected at the end of each infusion period. Plasma gastrin was then plotted against acid output by computer generated Langmuir Plot to give the D50 (sensitivity to gastrin) and E-max (PCM). CCK simultaneously stimulates acid secretion via the gastrin (CCKB) receptor and inhibits it by stimulating somatostatin release via the CCKA receptor on D cells in body mucosa. The maximal acid output (MAO) to CCK8 as percentage of MAO to G17 is thus a measure of somatostatin mediated inhibitory control.

Results:	HP-ve HVs	HP+ve HVs	HP+ve DUs
E-max (mmolh ⁻¹)	35.3 (21.3-67.3)	38.5 (17.2-65.0)	47.3* (18.2-73.7)
D50 (ngL ⁻¹)	75.1 (17.7-410)	164.0** (44.8-368)	69.8 (26.2-142)
MAO/CCK	26.2%	16.2%***	36.6%
MAOG17	(5.9 - 85.8)	(0-46.9)	(21.5-58.2)

Values are medians with ranges in parenthesis. *Indicates different from *H.P.*-ve HV at $p < 0.05$. ** Indicates different from *H.P.*-ve HV at $p < 0.001$. *** Indicates different from *H.P.*+ve DU at $p < 0.02$.

The higher acid response to gastrin in *H.P.*+ve DU patients versus infected *H.V.* is predominantly due to a reduced sensitivity to gastrin in the infected HVs when compared with both DU patients and uninfected HVs (i.e. true normals). This reduced sensitivity to gastrin in the infected non-ulcer subjects may be due to *H. pylori* body gastritis. The DU patients also had a slightly increased PCM. There was no evidence of impaired CCK mediated inhibitory control of body function in the DU patients. The apparently enhanced inhibitory control in the *H.P.*+ve HV can be explained by their lesser sensitivity to gastrin.

Conclusion: The two-fold difference in acid response to gastrin stimulation in the *H.P.*+ve DU patients versus *H.P.*+ve HV is predominantly due to impaired sensitivity to gastrin in the infected HVs.

W13

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND *HELICOBACTER PYLORI* AS INDEPENDENT RISK FACTORS FOR PEPTIC ULCER BLEEDING GM Hawkey, S Everitt, GM Pearson, WA Stack, CJ Hawkey. GI Trial Service, Division of Gastroenterology, University Hospital, Nottingham NG7 2UH, UK.

INTRODUCTION: Non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* both cause peptic ulcer and its complications. Indirect and retrospective data, however, suggest that these two factors may act independently. The Nottingham "NSAID or Helicobacter Outcomes as Peptic Emergency Referral" Study is a large ongoing investigation of the interaction of NSAIDs and *H. pylori* in peptic ulcer bleeding.

METHODS: Drug history (structured interview) and *H. pylori* serological status (Premier ELISA) were established prospectively in consecutive patients and hospital controls. The controls were matched for age and sex and selected to avoid distortion of background population NSAID usage. We report data from the first 256 subjects.

RESULTS: Cases and controls were well matched for age (Table) and sex. *H. pylori* infection and NSAID use was significantly higher in cases than controls. These subjects were more likely to have a past history (PH) and to report pain prior to admission.

	Mean Age	Hp+	NSAID	PH	Pain
Controls	68	48.1%	28.3%	13.5%	21.7%
Cases	66	77.8%**	53.8%	24.8%*	62.1%***

*p<0.05, **p<0.01, ***p<0.001

ABO blood group did not differ significantly between cases and controls. Twenty-three percent of patients positive by serology had a negative CLO test, not explained by recent drug use. Half of the NSAID usage in both cases and controls was aspirin, often as low dose cardiovascular prophylaxis.

Logistic regression analysis identified *H. pylori* and NSAIDs as the main determining factors. The relative risk associated with NSAID usage was 4.23 (95% CI 1.47-12.15, p=0.01), with *H. pylori* 2.78 (0.98-7.97, p=0.06) and for the interaction 0.18 (0.02-1.48, p=0.11).

CONCLUSIONS: NSAID exposure remains high, is now often due to aspirin and causes substantial ulcer morbidity. *H. pylori* is a significant risk factor which may be under-diagnosed by CLO test in bleeding patients but which shows no evidence of positive synergy with NSAID usage.

W15

THE NATURAL HISTORY OF NON-NSAID GASTRIC ULCER DISEASE FOLLOWING *H. PYLORI* ERADICATION: A ONE YEAR FOLLOW-UP STUDY IN THE AFRICAN SETTING. JA Louw, AK Cariem, TA Winter, W Osler, W Lucke and IN Marks. Gastrointestinal Clinic and Department of Medicine, University of Cape Town and Groote Schuur Hospital.

Eradication of *H. pylori* has been shown to prevent duodenal ulcer relapse. The effect of eradication on the natural history of gastric ulcer disease has been less well documented, even though it is now accepted that the majority of non-NSAID dependent gastric ulcers are *H. pylori* related. This study was done to determine the effect of *H. pylori* eradication on gastric ulcer recurrence rates following healing, in an environment with a high "background" prevalence of *H. pylori*.

PATIENTS AND METHODS: Patients with endoscopically proven, *H. pylori* positive gastric ulcers, without a history of significant salicylate or NSAID use, were eligible for study. Patients were endoscoped at entry to study, following 4 and 8 weeks of therapy (if not healed at four weeks), four weeks following documented healing and 6 and 12 months later, or whenever symptoms suggested a relapse. *H. pylori* status was determined by histology (2 antral and 2 body biopsies) and RUT (antral biopsy). Quadrantic biopsies were taken from the ulcer edge for histological evaluation. Patients were treated with omeprazole, 20mg bd for a month and received amoxicillin, 1g bd during the first or second two weeks of omeprazole therapy. Patients not healed after four weeks of treatment received a further four weeks of omeprazole and were not eligible for study if they were not healed at eight weeks.

RESULTS: Fifty one patients were entered. Of these, 13 did not qualify for study: 3=*H. pylori* negative, 3=gastric carcinoma, 4=not healed, 1=adverse drug event, 1=pyloric channel ulcer on review and 1=default. Data from 38 patients could be analysed.

	TOTAL	RELAPSED	p
Eradicated:	22	2 (9%)*	
Not eradicated:	16	8 (50%)	<0.01, Fishers exact

*One used salicylates for intercurrent problem. One of 22 subjects was found to be re-infected at the 6 month endoscopy.

CONCLUSION: *H. pylori* eradication protects against gastric ulcer relapse in patients not taking salicylates or NSAIDs, even in an environment of a high background prevalence of *H. pylori*.

W14

ULCER DEVELOPMENT IN LONG TERM NSAID USERS IN THE PRESENCE OR ABSENCE OF GASTRIC NEUTROPHILS. A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY. A S Taha, S Dahill, C Morran, N Hudson, C J Hawkey, F D Lee, R D Sturrock, R I Russell. Departments of Gastroenterology, Pathology, and Rheumatology, Royal Infirmary, Glasgow, and University Hospital, Nottingham, U.K.

The link between gastric neutrophils and NSAID ulcers remains unclear in humans, particularly the long term users of NSAID. To investigate the effect of base-line gastric mucosal neutrophils on future ulcer development in such patients, gastric antral biopsies were taken from 120 patients using NSAIDs, for a minimum of 4 weeks, who had no ulcers at base-line endoscopy. Patients were followed up with regular endoscopies for 6 months after being randomised, under double-blind conditions, to receive placebo, famotidine 20 or 40 mg bid for ulcer prophylaxis. Biopsies, carrying code numbers, were analysed for neutrophil count (0-3/field), other inflammatory cells and features, and for *H. pylori* (by histology, culture, and urease activity).

Results: The ulcer incidence at the completion of the study, in the absence (NEUT=0) or presence (NEUT>0) of neutrophils, was as follows:

	Placebo	Famotidine 20mg	Famotidine 40mg
NEUT=0. Ulcer incidence	7.7%	12.5%	0.0%
95% confidence intervals	0.0%-22.2%	0.2%-32.0%	0.0%-20.6%
Patients with ulcers	1/14	2/16	0/13
NEUT>0. Ulcer incidence	47.4%*	12.6%	13.0%
95% confidence intervals	28.5%-66.2%	0.0%-26.0%	2.8%-33.6%
Patients with ulcers	13/28	3/26	3/23

(*): P<0.001, log rank test. P=0.017, adjusted for treatment differences. Eight of 46 (8/46, 17%) patients without *H. pylori* had gastric neutrophils, compared with 69/74 (93%) with both *H. pylori* and neutrophils (P<0.001).

Conclusions: The presence of gastric mucosal neutrophils, with or without *H. pylori*, significantly increases the risk of future ulceration in long term NSAID users. However, neutrophils are more likely to exist in the presence of *H. pylori* gastritis.

W16

LOW GASTROINTESTINAL TOXICITY OF MELOXICAM, A SELECTIVE INHIBITOR OF THE INDUCIBLE CYCLOOXYGENASE (COX-2) ENZYME CJ Hawkey. Division of Gastroenterology, University Hospital, Nottingham NG7 2UH, UK, for the International MELISSA Study Group.

INTRODUCTION: Recognition of two cyclooxygenase (COX) isoforms has stimulated development of selective inhibitors of COX-2 (induced in inflammation and responsible for arthritic symptoms), which leave gastro protective COX-1 prostaglandin synthesis unimpaired. We compared meloxicam a selective COX-2 inhibitor with diclofenac for efficacy and safety.

METHODS: Patients with osteoarthritis requiring pain relief were randomised to receive meloxicam 7.5mg daily (n=4628) or diclofenac SR (n=4685) 100mg, both given once daily under double blind conditions for one month. Comparative efficacy was assessed by visual analogue scale, and other measures. All adverse events, including perforations, ulcers, bleeds (PUBs) and hospitalisations were rated for severity and relationship to drug.

RESULTS: Both drugs were equally effective (visual analogue scale for pain on active movement 30.3 ± 27ml meloxicam vs 32.5 ± 26ml for diclofenac) but meloxicam caused fewer adverse events.

	Meloxicam	Diclofenac
All adverse events	27%	32%***
Gastrointestinal adverse events	13%	19%***
Withdrawal, lack of efficacy	1.7%	1.0%
Withdrawal, GI adverse events	2.7%	5.9%***
PUBs (n)	5	7

**p < 0.001

There was significantly less dyspepsia, abdominal pain, nausea/vomiting and diarrhoea with meloxicam.

CONCLUSIONS: Meloxicam a selective COX-2 inhibitor, is as effective in osteo arthritis as diclofenac but associated with fewer GI adverse events.

W17

RESISTANCE OF HELICOBACTER PYLORI TO METRONIDAZOLE: AN IMAGINARY PROBLEM?

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Concern has been raised that *H. pylori* might exhibit both primary and secondary resistance to nitroimidazoles, making these drugs less useful in therapy.

In 1992/3 102 unselected patients not on antibiotics for at least 2 months had gastric antral forceps biopsies taken at gastroscopy. These were sent in transport medium for micro-aerophilic culture for 5-7 days, and then sub-cultured with antimicrobial discs for 3 days to test sensitivity. None were resistant to amoxicillin or tetracycline, 2 were resistant to erythromycin and clarithromycin, and 19 were resistant to metronidazole.

In 1996 94 patients had gastric antral forceps biopsies cultured. Antimicrobial sensitivity was assessed using E-test strips. Metronidazole sensitivity was tested with a 24 hour preliminary anaerobic culture. None were resistant to amoxicillin, 1 to tetracycline, 2 to clarithromycin, and only 2 to metronidazole.

RESULTS OF E-TESTING
(n = 94 patients)

ANTIBIOTIC	SENSITIVITY	MIC (mg/l) mode (range)
Amoxicillin	100%	0.016 (<0.016-0.64)
Tetracycline	99%	0.016 (<0.016-0.5)
Clarithromycin	98%	<0.016 (<0.016-0.016)
Metronidazole	98%	0.032 (0.002-6)

Because of the discrepancy 37 cultures were tested for metronidazole sensitivity using both micro-aerophilic disc culture and E-testing with preliminary anaerobic culture. Eight cultures showed apparent resistance to metronidazole on disc testing (MIC > 5 mg/l), but were all sensitive on E-testing (MIC 0.002-0.5 mg/l).

CONCLUSION. - Metronidazole resistance to micro-aerophilic disc testing is a laboratory artefact, not reflecting true insensitivity to therapy.

W19

HELICOBACTER PYLORI ERADICATION THERAPY COMPARED WITH RANITIDINE MAINTENANCE THERAPY IN PATIENTS WITH CHRONIC DUODENAL ULCER DISEASE: A PROSPECTIVE PHARMACOECONOMIC EVALUATION. A T Prach¹, M Malek², D Hopwood³, B W Senior⁴, F E Murray¹. University Departments of Clinical Pharmacology¹, Pathology³ and Medical Microbiology⁴, Ninewells Hospital, Dundee and Department of Management², University of St Andrews.

Although eradicating *Helicobacter pylori* (*Hp*) infection in duodenal ulcer (DU) disease is widely practised, there are few prospective studies evaluating the cost-effectiveness of this approach. The aim of this study was to compare the health care costs over one year in two groups of patients with chronic DU who received either *Hp* eradication therapy or maintenance therapy using ranitidine. **Methods.** Patients with active *Hp* infection were randomised to receive either 150mg ranitidine, daily [n = 58] or, *Hp* eradication [n = 61] using OAM (omeprazole 40mg/d, amoxicillin 2G/d, metronidazole 1.2G/d; for 14 days), or OC (omeprazole 40mg/d, clarithromycin 1.5G/d; for 14 days), if penicillin-allergic. Eradication patients underwent ¹³C urea breath testing to confirm success. Patients in both groups were managed according to good clinical practice and investigated if symptoms worsened. Health care costs in each group were quantified. **Results.** *Hp* eradication rates:-

	Per protocol		Intention-to-treat	
	Eradication rate	95% CI	Eradication rate	95% CI
OAM	58/58 (100%)	0.92-1.00	56/59 (94.9%)	0.85-0.99
OC	2/2 (100%)	0.20-1.00	2/2 (100%)	0.20-1.00
Overall	60/60 (100%)	0.92-1.00	58/61 (95.1%)	0.85-0.99

Two patients failed eradication therapy because of side-effects (and withdrew). Another did not attend for breath testing and was lost to follow-up. At one year, of those randomised to eradication therapy, 49/61 (80.3%; CI 0.68-0.89) no longer took ulcer-healing drugs. The mean annual per patient health care costs were: £249 for maintenance therapy and £217 for eradication therapy. **Conclusion.** *Hp* eradication saved £32 in the first year of treatment. The saving in subsequent years is likely to be much greater because of reduced ulcer-healing drug prescribing and investigation costs.

W18

THE OPTIMUM 5 DAY THERAPY AGAINST HELICOBACTER PYLORI.

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Introduction: *H. pylori* therapy is usually given for at least 7 days. A shorter regimen would be cheaper and better tolerated. We have investigated the optimum 5 day therapy with various combinations of lansoprazole 30 mg bd (L), clarithromycin 250 mg bd (C), amoxicillin 1 g bd (A) and metronidazole 400 mg bd (M). **Methods:** Patients attending the dyspepsia clinic who were *H. pylori* positive as assessed by histology, rapid urease test, microbiology and ¹³C-urea breath test (¹³C-UBT) were randomised to receive 5 days of either LCM, LAC or LACM. The investigator was blinded to the treatment group. Success of treatment was evaluated by ¹³C-UBT at least 4 weeks after completion of therapy. **Results:** 143 patients were recruited to the study (mean age 53 ± 14 years, range 21-80, 52% male). Culture was successful 84% of cases with 51% harbouring metronidazole resistant strains. There was no statistical difference in age, gender or smoking between the 3 groups. Eradication rates were higher in the LCM group (38/45 - 84%) than the LAC group (29/47 - 62%; p=0.02 Fisher's exact test). LCM was less effective against metronidazole resistant organisms (eradication rate 13/19-68%) than sensitive organisms (13/14 - 93%). Treatment was successful in 46/51 (90%) patients taking LACM. There was a trend towards adverse events being more common in the LACM group (50%) than the LCM or LAC groups (36%) but this did not reach statistical significance (p=0.2 χ^2). **Conclusions:** LCM is more effective than LAC in eradicating *H. pylori*. Adding amoxicillin to LCM may improve efficacy but increase adverse events. Five days of LCM appears as efficacious as 7 day regimens for metronidazole sensitive strains of *H. pylori* but is less effective against resistant organisms.

W20

RANITIDINE BISMUTH CITRATE PLUS CLARITHROMYCIN AND TETRACYCLINE: A SEVEN-DAY HELICOBACTER PYLORI ERADICATION REGIMEN. M Williams, J Sercombe, R E Pounder, Royal Free Hospital School of Medicine, London NW3 2QG.

Introduction: The ideal regimen for treating *Helicobacter pylori* (*H. pylori*) infection needs to be simple, short duration and well tolerated. It should give reproducible and high levels of eradication on an "intention-to-treat" basis. Dual therapy with ranitidine bismuth citrate plus clarithromycin for fourteen days is a highly effective regimen for eradicating *H. pylori* infection.

Aim: To determine whether, with the addition of a second antibiotic, it may be possible to reduce the duration of treatment with ranitidine bismuth citrate to seven days and yet maintain a high eradication rate.

Methods: A total of 48 dyspeptic patients were enrolled to this open treatment study. All were infected with *H. pylori*, as determined by ¹³C urea breath test +/- a rapid urease test at endoscopy. Patients were treated with twice daily ranitidine bismuth citrate 400mg, clarithromycin 500mg and tetracycline hydrochloride 500mg, all for 7 days. *H. pylori* eradication was assessed by ¹³C urea breath test at least 28 days after the completion of treatment. Adverse events were assessed by patient interview with all events mentioned, either spontaneously or on direct questioning, considered significant.

Results: Successful eradication of *H. pylori* was achieved in 43/48 (90%). Compliance was >90% in 47/48 (98%): 1 patient stopped treatment after 2 days due to vomiting. Minor adverse events were reported by 24 of the remaining 47 patients (51%) - these were loose stools (31%), nausea (17%), taste disturbance (10%), vomiting (2%), sore mouth (2%) and vaginal candida (2%).

Conclusion: Triple therapy with ranitidine bismuth citrate 400mg, clarithromycin 500mg and tetracycline 500mg, all twice daily for seven days, is a safe well-tolerated treatment regimen that eradicates *H. pylori* infection in 90% of patients on a strict intention-to-treat analysis.

W21

EFFECT OF *H. PYLORI*, ASPIRIN & ANOXIA ON ANTIBIOTIC PERMEABILITY IN THE RAT STOMACH. AF Goddard, PO Erah, JC Atherton, PN Shaw, DA Barrett & RC Spiller. Division of Gastroenterology, University Hospital, Nottingham. UK.

Background The flux of amoxicillin (AMO) across normal gastric mucosa *in vivo* and *in vitro* is 10% that of metronidazole (MET). The effect of gastric mucosal injury (as in *H. pylori* (*Hp*) gastritis) on the flux of either antibiotic is unknown.

Aims To study the effect of mucosal injury caused by toxigenic and non-toxicogenic *Hp* strains on the gastric mucosal flux of MET and AMO and compare this with the effect of aspirin and anoxia.

Methods Gastric mucosal flux (nmol.hr⁻¹.cm⁻²) was assessed using a previously validated Ussing chamber method. Serosal to mucosal flux from 1mM solution of antibiotic was measured over 60 min under baseline (control) conditions and with the following added to the mucosal chamber (n=8): 1) sonicate of a toxigenic *cagA+* *Hp* isolate from a DU patient (J258); 2) sonicate of a non-toxicogenic *cagA-* *Hp* isolate (Tx30a); 3) 2mM aspirin; 4) 20 mM aspirin; 5) N₂ instead of O₂/CO₂, thus making the mucosa anoxic. Fluxes were compared using non-parametric analysis. Light microscopy was performed to assess mucosal damage.

	Flux [mean(SEM)]		Histological Damage
	Amoxicillin	Metronidazole	
Control	2.4 (0.3)	20.3 (3.5)	none
J258 (<i>cagA+</i>)	2.5 (0.6)	35.6 (3.1)**	minimal
Tx30a (<i>cagA-</i>)	2.1 (0.3)	17.8 (1.5)	minimal
Anoxia	4.7 (0.8)*	25.3 (4.2)	severe
2 mM aspirin	<0.3***	21.2 (7.7)	severe
20 mM aspirin	<0.3***	17.9 (1.6)	severe

* P<0.02, ** P<0.01, *** P<0.001

Conclusions 1) AMO permeates gastric mucosa by a different pathway than MET. 2) Toxigenic *cagA+*, but not non-toxicogenic *cagA-*, *Hp* increases MET permeation *in vitro*. 3) Increased MET permeation is not secondary to epithelial cell junction damage (which is maximal in anoxic and aspirin treated tissue).

AFG is in receipt of an Astra Research Fellowship

W23

ROLE OF HELICOBACTER PYLORI IN GASTRIC ADAPTATION TO REPEATED ASPIRIN ADMINISTRATION IN MAN. J.W. Konturek, A. Dembinski, W.Fuchs, J.Elbert, S.J. Konturek and W. Domschke. Department of Medicine B, University of Münster, Münster, Germany, Institute of Physiology, Jagiellonian University, Kraków, Poland, Takeda Pharma, Aachen, Germany.

Background: The phenomenon of gastric adaptation after repeated exposures to ASA is well documented in animals and in humans. The role of *Helicobacter pylori* (*H.pylori*) as a possible pathogenic factor of NSAID-induced gastropathy remains controversial. **Aim:** This study was designed 1) to evoke the gastric adaptation in response to repeated exposure to ASA in the same subjects before and after eradication of *H.pylori* and 2) to examine the morphological and functional changes of gastric mucosa during the 14 days treatment with ASA in subjects with and without the presence of *H.pylori* infection. **Material and Methods:** Eight healthy volunteers (age 19-27) with *H.pylori* infection and no gastrointestinal symptoms, were given ASA 1g b.i.d. during 14 days. Mucosal damage was evaluated by endoscopy on the 3rd, 7th and 14th day using modified Lanza score. During each endoscopy mucosal blood flow was measured using laser-Doppler flowmeter. Mucosal biopsies were obtained for estimation of DNA synthesis by measuring ³H-thymidine incorporation into DNA. Prior to each endoscopy the gastric microbleeding was determined in three consecutive gastric washings. Three months after successful eradication of *H.pylori* (amoxicillin + clarithromycin + lansoprazole) confirmed by ¹³C-urea breath test and mucosal rapid urease (CLO) test the same subjects received again the 14 days treatment with ASA at the same dosage and underwent the same examinations as prior to the antimicrobial therapy (lansoprazole+ amoxicillin+clarithromycin). **Results:** In subjects with *H.pylori* infection ASA induced acute gastric mucosal damage mainly in gastric corpus; the endoscopic Lanza score reached maximum at 3rd day and remained unchanged at 7th and 14th day of ASA treatment. After *H.pylori* eradication ASA-induced acute gastric mucosal damage also reached its maximum at 3rd day but then declined to fall on day 14 to about 25% of initial peak thus confirming the occurrence of adaptation. Mucosal blood flow was significantly higher before than after *H.pylori* eradication and in both cases it significantly increased on 3rd and 7th day. Before ASA administration DNA synthesis was similar in subjects before and after eradication of *H.pylori*, however the DNA synthesis rate showed significant increase on day 7 of ASA administration only in *H.pylori* eradicated subjects. Gastric microbleeding reached its maximum on the 3rd day of ASA treatment being significantly higher in *H.pylori*-eradicated subjects than in those with *H.pylori* infection. This microbleeding decreased to almost normal values by the end of the study in *H.pylori*-eradicated subjects but remained significantly elevated in *H.pylori* infected subjects. **Conclusions:** 1) Gastric adaptation to ASA is impaired in *H.pylori*-positive subjects but eradication of *H.pylori* restores the adaptation and 2) DNA synthesis and possibly also mucosal cell turnover in response to ASA are suppressed in *H.pylori*-infected patients and this can be reversed by eradication of *H.pylori*.

W22

FACTORS ASSOCIATED WITH HELICOBACTER PYLORI INFECTION AND DUODENAL ULCERS IN PATIENTS ATTENDING ENDOSCOPY.

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Helicobacter pylori (*H. pylori*) is associated with peptic ulcer disease. However, associations with *H. pylori* infection itself and with duodenal ulcer (DU) disease itself need to be compared and evaluated for their aetiological significance.

450 case-notes of unselected patients attending the Endoscopy Clinic during the period 1993/94, were retrieved and the following variables were recorded:- sex, age, smoking; diagnosis as DU, oesophagitis, non-ulcer dyspepsia (NUD), other macroscopic lesions; number of endoscopies; previous and present record of diagnosis and treatment of *H. pylori* infection. The results, analysed by logistic regression analysis, were:

1. Associated with DU: 2. Associated with *H. pylori*:

factor	p <	factor	P <
age	0.001	sex(male)	0.0001
smoking	0.0001	no.endoscopies	0.0001
<i>H. pylori</i>	0.0138	oeso.(neg.)	0.0043
no.endoscopies	0.0122	NUD	0.0236
		DU	0.0156

Conclusions: Smoking remains strongly associated with DU. Oesophagitis is negatively associated with *H. pylori*. It is interesting however, that the number of endoscopy a patient has undergone positively influence *H. pylori* status. The nature of this link between *H. pylori* infection and the number of endoscopies is uncertain and requires further investigation, but these facts support a previously published study.

W24

MOTILITIES OF ULCER AND NON-ULCER ASSOCIATED STRAINS OF Helicobacter pylori. M Worku, L Ashton, RL Sidebotham*, RPH Logan* and QN Karim, Departments of Microbiology and Gastroenterology*, St. Mary's Hospital Medical School, London.

Background Motility is a colonization factor for *Helicobacter pylori* (*Hp*), presumably because it enables the bacterium to cross the viscid mucus layer to the mucosal surface where it damages epithelial cells by attachment and cytotoxin release. The density of *Hp* at the mucosal surface in the gastric antrum is significantly greater in patients with duodenal ulcer (DU) than with non-ulcer dyspepsia (NUD). We have investigated whether this important difference in colonization is due to an inherent difference in motility between ulcer and non-ulcer associated *Hp* strains.

Methods *Helicobacter pylori* were isolated from endoscopic biopsies of patients with DU and NUD and cultured in presence of 8% CO₂ at 37°C in brain heart infusion broth supplemented with calf serum and made selective with antibiotics. Bacterial motility was quantitatively measured in real time with a Hobson BacTracker in broth (DU n = 14; NUD n = 13) at different phases of the growth cycle, and also in methyl cellulose (MC) of molecular weight 14 Kd (DU n = 6; NUD n = 6), ranging in viscosity from 5 - 50 centipoises (cp) to simulate the high viscosity of the gastric mucus layer. Data are reported as curvilinear velocity (CLV, μm/s), straight line velocity (SLV, μm/s) and track linearity (ratio SLV/CLV). Statistics are by Mann-Whitney U-test.

Results (1). Motilities of *Hp* from DU and NUD patients, when expressed as CVL and track linearity, were not significantly different from each other when measured in broth or in MC. (2). *Helicobacter pylori* were, however significantly (p < 0.01) more motile in broth when in log-phase than in lag or stationary phases of growth [mean CLV; lag phase 5.9 (DU) and 5.9 (NUD) μm/s, log phase 28.7 and 28.4 μm/s, stationary phase 6.3 and 6.4 μm/s]. (3). Motility of *Hp* in log-phase decreased significantly (p < 0.01) when the bacteria were transferred from broth (mean CLV 28.9 (DU) and 26.8 (NUD) μm/s), to MC viscosity 30 cp (mean CLV 5.7 and 5.8 μm/s), and ceased in MC viscosity 50 cp (mean CLV 4.7 and 4.9 μm/s - Brownian movement only). (4). Track linearity of *Hp* in log phase was also significantly greater (p < 0.01) in MC viscosity 30 cp [0.91 (DU) and 0.89 (NUD)] than in broth (0.38 and 0.34).

Conclusion The greater density of *Hp* at the antral mucosal surface in DU patients when compared with NUD patients is not due to an inherent difference in motility of the ulcer and non-ulcer associated strains: log phase *Hp* exhibit slow-linear motility in high viscosity medium irrespective of source.

W25

BACTERIAL CagA STATUS IS UNRELATED TO GASTRIC FUNCTION INDEXES OR TO THE TYPE EITHER SEVERITY OF SYMPTOMS IN PATIENTS WITH H.pylori-POSITIVE NON-ULCER DYSPEPSIA (NUD).

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It has been widely shown that H.pylori (HP) infection induces disturbances of gastric function in patients (pts) both with duodenal ulcer and NUD. Little is known, however, about a possible relationship between such disturbances and the bacterial strains. Aim of this study was to assess whether gastric function parameters and dyspeptic symptoms are related to CagA status.

Methods. 38 consecutive pts with HP-positive NUD were examined. They had suffered from dyspepsia for > 6 months and none of them had macroscopic lesions at upper GI endoscopy. HP positivity was determined by means of histology and urease rapid test on antral biopsies and ¹³C-urea breath test. No pt had undergone previous anti-HP therapy and any medication was discontinued at least 3 weeks prior to the study. Dyspeptic symptoms were classified into 3 different categories according to the predominant complaint, and scored for severity from 0 to 3. In all subjects basal (BAO) and pentagastrin stimulated acid output (MAO), fasting and meal-induced gastrin concentrations, fasting pepsinogen I (PG I) levels and gastric emptying of solids (by means of ultrasounds) were measured. CagA status was determined indirectly by assaying serum CagA IgG antibodies by commercial Western-Blotting (Helico-Blot, Genelabs).

Results. 17 of 38 NUD pts were CagA seropositive (45%). Mean BAO and MAO values of CagA seropositive pts (3.0±2.8 and 20.4±7.6 mmol/h, respectively) were comparable to those of seronegative pts (3.8±2.5 and 23.5±7.3). No significant differences were found in fasting (55.9±14.4 vs 57.2±11.6 pg/ml) and stimulated gastrin levels [23370 (AUC) vs 21719] between the two groups. Similarly, gastric emptying of solids as well as the type and severity of dyspeptic symptoms did not significantly differ in the two groups of pts. In contrast, fasting PG I levels were higher in seropositive than seronegative pts (98.8±33 vs 79.4±32.6 ng/ml, p=0.07), concomitantly with a higher degree of antral inflammation at histology.

Conclusions. Our findings indicate that gastric function disturbances associated with HP infection and the type and severity of symptoms in NUD pts are independent of bacterial CagA status.

W27

DETECTION OF HELICOBACTER PYLORI FROM GI SECRETIONS USING PCR.

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Introduction- Oral-oral and oral-faecal spread have been suggested as the route of transmission of *Helicobacter pylori* (HP). However, the source and route of transmission remain largely unknown.

Aim- To investigate secretions from the upper GI tract for transmission potential in HP infection.

Method- Sixty patients referred for routine endoscopy for dyspeptic symptoms were studied. 3 gastric biopsies were taken for culture and the rapid urease test. Gastric juice and duodenal (D2) aspirate were collected for culture and PCR.

Results-HP prevalence (%), n = 60

	Culture	PCR	Urease test
Gastric biopsy	20(33%)	33(55%)	21(35%)
Gastric juice	0	9(15%)	-
Duodenal asp.	0	5(8%)	-

In summary, HP could not be cultured from the secretions, but it was cultured from 33% of the gastric antral biopsies. In 8 and 15% of patients, PCR for HP was positive in the duodenal and gastric secretions respectively, but only after centrifugation to produce pellets. These patients were also positive by culture of the biopsies.

Conclusion- Gastrointestinal secretions may harbour *Helicobacter pylori* and play a significant role in the transmission, especially in vomiting and diarrhoeal diseases. However, it is not known whether the PCR-detected organisms were dead or alive.

W26

CULTURING H. PYLORI FROM GASTRIC ASPIRATES: THE EFFECT OF ACID IN VIVO AND IN VITRO. M Williams¹, A Lawson¹, E Slater², R J Owen², R E Pounder¹, ¹Royal Free Hospital School of Medicine, London, ²Central Public Health Laboratory, London.

Introduction: Attempted culture of *H. pylori* (Hp) from gastric aspirates yields poor results. Could increased intragastric pH release Hp from the gastric mucosa into the lumen, facilitating Hp culture from gastric aspirates?

Methods: 6 serial morning gastric aspirates, 3 before and 3 during dosing with omeprazole 40mg bid, were obtained from each of 11 healthy volunteers. 10 were infected with Hp and 1 non-infected, as determined by serology and ¹³C urea breath test. Aspirates were taken after an overnight fast, via a nasogastric tube inserted 10 min prior to sampling. pHmetry was performed on each aspirate. 5 ml of aspirate was added to *Helicobacter* transport medium for culture within 2 hours. Culture was performed blind as to Hp and dosing status. Aspirates were incubated with Sputosol, centrifuged and the resulting pellet resuspended in maximum recovery diluent (MRD). Portions of resuspended aspirate were diluted for 5 min either with 1:10 MRD or with 1:10 HCl-KCl buffer (pH 2.2) to reduce contamination with upper respiratory tract flora (URTF). Aliquots from both were inoculated on 10% Columbia and Dents selective agar. Hp was identified by morphology, urease activity and detection of the *ureA/B* genes by PCR.

Results:	Maximum Recovery Diluent (n=60)		HCl-KCl Buffer (n=56)	
	POS (%)	NEG (%)	POS (%)	NEG (%)
Before omeprazole	14 (47)	16 (53)	20 (77)	6 (23)
During omeprazole	3 (10)	27 (90)	20 (67)	10 (33)

HCl-KCl buffer gave significantly higher yields of Hp compared to MRD, both before (p=0.02) and during (p<0.0001) omeprazole dosing. Omeprazole reduced the yield of Hp with MRD (p=0.002) but had no effect with HCl-KCl (p=0.4). All Hp infected subjects yielded at least 1 positive aspirate for HCl-KCl, whilst 2 subjects yielded no positive aspirates for MRD. Aspirates from the uninfected subject were all negative by both methods.

Conclusions: 1. Isolation of Hp from the gastric aspirates of Hp infected subjects is inhibited by URTF overgrowing Hp colonies. 2. The addition of acid *in vivo* facilitates the isolation of Hp, by inhibiting URTF. 3. Decreasing intragastric acidity *in vivo*, using omeprazole, does not affect the isolation of Hp using the HCl-KCl method. This suggests that the apparent inhibition of Hp culture by omeprazole is due to competition from URTF.

W28

PROLONGED ACID SUPPRESSION THERAPY AND PROXIMAL MIGRATION OF HELICOBACTER PYLORI. H Ihmaidat¹, CK MacKay, H Kasem, CR Carter, J Going², JF MacKenzie², RC Stuart.

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Intestinal metaplasia at the oesophago-gastric junction (OGJ), present in 15-30% of dyspeptic patients is a risk factor for adenocarcinoma.

Aim: to investigate whether *Helicobacter pylori* (Hp) or prolonged acid suppression therapy is associated with intestinal metaplasia at the OGJ.

Method: At diagnostic endoscopy, biopsies were taken from gastric antrum, body and OGJ in 190 patients. None had Barrett's oesophagus. Hp status was assessed using Cresyl Violet stains. Intestinal metaplasia was defined as the presence of Goblet cells seen on Haematoxylin & Eosin and Periodic Acid Schiff/ Alcian Blue stains. Patients were interviewed regarding duration of acid suppression therapy. **Results:** 62 patients had intestinal metaplasia at the OGJ, with Hp at the antrum in 65% and OGJ in 43.5%. This compared with 42.3% (p<0.01) and 29.7% (p=0.13) respectively in the 128 normal patients.

Helicobacter pylori status

Acid Suppression Therapy (Months)	Antrum +ve & OGJ -ve		Antrum +ve & OGJ +ve		Antrum -ve & OGJ -ve
	& OGJ -ve	& OGJ +ve	& OGJ -ve	& OGJ +ve	
Total	3.5*	24*	12	12	
	(0-180)	(0-216)	(0-192)	(0-192)	
Normals	4	20	12	12	
	(0-180)	(0-216)	(0-192)	(0-192)	
Intestinal Metaplasia	2	24	15	15	
	(0-144)	(0-204)	(0-168)	(0-168)	

Values: Median(range); *p<0.05 by Mann-Whitney U test.

Conclusion: Patients with intestinal metaplasia at the OGJ are significantly more likely to be *Helicobacter* positive. There is evidence of proximal migration of *Helicobacter* in these patients. Prolonged acid suppression therapy favours the migration of *Helicobacter pylori* into the proximal stomach. H. pylori eradication should be considered before starting maintenance acid suppression therapy.

W29

A NEW MINIMALLY INVASIVE SURGICAL TECHNIQUE FOR GASTRIC LEIOMYOMAS.
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A new surgical technique has been developed for dealing with gastric leiomyomas. This is performed under a general anaesthetic and with the patient supine. The patient is gastroscopied to assess the position of the leiomyoma. A 30 degree telescope is then inserted through a 10mm umbilical port. The stomach is visualised and a suture is passed through the anterior abdominal wall directly over the anterior aspect of the stomach. This suture is then passed through the anterior wall of the stomach and then back through the anterior abdominal wall. A second suture is passed in the same way adjacent to the first. Traction on these sutures therefore lifts up the anterior wall of the stomach. A 10mm port is placed under direct vision in the left upper quadrant. Using cutting diathermy a transverse incision is made through the anterior wall of the stomach below the sutures. Visualisation by means of the gastroscope ensures that the incision is placed allowing best access to the leiomyoma. The gastric leiomyoma can then be seen and grasped by Johannes laparoscopic graspers. A second port (12mm) is positioned in the right upper quadrant. Through this can be placed an endoscopic linear cutter. Traction on the laparoscopic graspers pulls the leiomyoma through the transverse incision in the stomach. The linear stapler can then be placed across the stomach beneath the leiomyoma. Sequential applications and firings of the linear stapler removes the leiomyoma and simultaneously closes the stomach. The anterior gastrotomy is closed with a single layer of maxon.

Results Eight patients, median age 77 years (range 33-83 years) who have presented with gastric leiomyomas have been treated. No deaths or complications occurred. One patient required conversion to an open procedure as the leiomyoma was very large. Following this procedure patients are mobilising and allowed to drink and eat the following day. The median length of stay in hospital was 5 days (range 4-7 days). The patient requiring the open procedure remained for 8 days. No peri or post operative blood transfusion was required.

Conclusions This is a safe and effective technique. It allows earlier mobilisation than conventional laparotomy.

W31

LONG-TERM SURVIVAL, SYMPTOMS AND DRUG USE AFTER PEPTIC ULCER HAEMORRHAGE

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Although peptic ulcer is the commonest source of upper GI bleeding there are no unselected published data on the long-term follow up.

Over a 2 year period out of a whole community population of 468,000, 414 patients (421 admissions) bled from peptic ulcers and were admitted to a single dedicated unit in Aberdeen. Of 414 patients 406(98.1%) were followed up (mean 29.8 months) and a detailed questionnaire completed.

The 30 day mortality was 7.2% (mean age 79 yrs). A further 71 deaths during follow up gave an overall mortality of 24.8%. The mean age at death was 76 years. Life table analysis, comparing age and sex matched controls, revealed an excess mortality in the peptic ulcer group but only in the first year of follow-up, and by 5 years the overall mortality was equal. Only one death due to bleeding occurred after 30 days. Consumption of Aspirin and NSAID in combination (odds ratio 2.4 (1.0-5.6)) but not individually, and bleeding with no prior abdominal pain (odds ratio 1.7 (0.9-3.3)) were associated with reduced survival.

At follow-up 50.6% of patients had no dyspepsia. Maintenance acid suppression therapy was prescribed for 58.4% of patients. Of those cardiovascular disease patients on low dose aspirin (14.3%), acid suppression therapy was co-prescribed in 74.3%. Only 2.4% patients were on NSAIDs. None were on high dose aspirin nor aspirin plus NSAID combination. This contrasts with 21% taking acid suppression therapy and 45% taking aspirin or NSAID at the time of their initial presentation.

Twenty-three(9.4%) patients reported upper GI bleeding during follow-up but only 6 (2.4%) required further hospital admission.

In the long-term the majority of patients are asymptomatic. Recurrent bleeding is rare. After peptic ulcer haemorrhage both early and late mortality are principally related to concurrent disease in an elderly population. Compared to controls there is an initial increased mortality rate which is not sustained past the first year, and by 5 years survival is identical.

W30

THE CHANGING PATTERN OF OESOPHAGO-GASTRIC CANCER.

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The aims of this study were to seek objective evidence for clinically perceived changes in the anatomical distribution and age of presentation of cases of oesophago-gastric malignancy.

The records of the Northern Region Cancer Registry over a ten year period from 1984 were examined for oesophageal and gastric cancer registration. Data for age at diagnosis and precise site of tumour were extracted. Incidence was calculated from published annual OPCS local population statistics. Change of quinquennial incidence and age at presentation were analysed by the unpaired t-test. Results are given as mean (sem)

10,872 complete oesophago-gastric cancer registrations were identified. The mean annual incidence of oesophago-gastric cancer over the 10 year period was 34.4 cases per 100,000 population and the mean age of diagnosis was 72 (range 18-100); neither changed significantly over the period of the study. The incidence of oesophageal cancer rose from 9.82 (0.37) cases per 100,000 in the period 1984 to 1988 to 11.24 (1.81) cases per 100,000 in the period 1989 to 1991 (P=0.17). The incidence of gastric cancer fell slightly from 25.3 (0.57) cases per 100,000 to 22.4 (2.88) cases per 100,000 (P=0.10). Pyloric and antral cancers fell markedly in incidence from 2.13(0.70) to 0.84(0.12) cases per 100,000 (P=0.02). The ratio of gastric cardia to pyloric/antral cancers rose from 1.08 to 2.03 (P=0.01) over the two five year periods. Patients with cardia cancers were diagnosed at a consistently younger age than patients with distal gastric cancer (68.8 (0.53) vs 71.4 (0.48) years P=0.002). Lower third oesophageal cancers were diagnosed at a similar age to cardia patients (69.4 (0.45) years; P=0.4) and similarly earlier than distal gastric cancer patients (P=0.007).

The pattern of oesophago-gastric cancer has changed in the period 1984 to 1993; distal gastric cancer has become less common. Patients in the proportionally increasing group with adenocarcinoma of the cardia and cardio-oesophageal junction have a younger age of presentation.

W32

DENTAL PLAQUE AS A RESERVOIR FOR HELICOBACTER PYLORI (HP): DOES IMMUNOCHEMISTRY ANSWER THE QUESTION?

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Presence of HP in dental plaque is controversial, a discrepancy attributed to differences in methodology. Our aim was to validate and apply for the first time an immunochemical technique to detect HP in dental plaque.

80 consecutive patients (M:F=44:36, age range 16-87 years) undergoing endoscopy were examined for oral hygiene and a sample of dental plaque was removed before the procedure. Subjects on antibiotics or using antiseptic mouth-washing were excluded. Oral hygiene was classified using the Loe and Silness plaque and gingival index. Dental plaque was obtained with a sterile Gracey curette, from at least 5 dental elements, suspended in sterile saline, smeared on a slide, dried, fixed in ethanol 90° and stored at -4°C until examination.

All patients had six biopsies taken from antrum, body and fundus for microscopic examination and a sample of blood for detection of HP antibodies. Plaque smears were tested by indirect immunoperoxidase technique based on a mixture of two monoclonal antibodies specific for HP (Negrini R. Gastroenterology 1989;96:414-20); its sensitivity and specificity were both 100% when tested on plaque samples artificially enriched with HP.

51 patients (64%) were HP infected, as diagnosed by concordant histology and serology. All of them had variable degree of active chronic gastritis on microscopy and 15 had peptic ulcer. In none of these infected patients was HP detected in dental plaque. Furthermore the 400 dental plaque samples from the whole study population were all HP negative. No relationship was found between oral hygiene scores and presence of HP in the stomach.

In conclusion, our results using a highly sensitive method for detection of HP in dental plaque suggest that plaque is not a reservoir for HP infection.

Small bowel and pancreas W33-W47

W33

SMALL INTESTINAL CRYPT HYPERPLASIA IN AFRICAN TROPICAL ENTEROPATHY. AM Veitch¹, P Kelly¹, N Luo², I Segal³, SK Spies⁴, MJG Farthing. ¹Digestive Diseases Research Centre, St Bartholomew's & The Royal London School of Medicine & Dentistry, London, ²University Teaching Hospital, Lusaka, Zambia & Gastroenterology divisions of the Universities of ³Witwatersrand and ⁴Pretoria, South Africa.

Introduction and aims: We have previously found evidence of tropical enteropathy in the healthy black population of Lusaka, Zambia, but normal villous architecture in urban black South Africans. In addition, we have demonstrated increased mucosal T cell activation in the Zambian population compared to South Africans. In this study we have sought to determine whether, like other T cell-mediated enteropathies, tropical enteropathy is associated with crypt hyperplasia.

Patients and methods: 12 black Zambian subjects, 22 black South Africans and 21 white South Africans undergoing routine upper gastrointestinal endoscopy for dyspepsia (GU, DU, diarrhoea and AIDS excluded) were studied. Formalin-fixed paraffin-processed biopsies were assessed by computerised image analysis to determine villous height (VH) and crypt depth (CD). Duodenal biopsies, fixed in Carnoy's solution and stored in 70% ethanol, were stained by the Feulgen reaction. Crypt mitotic counts were determined by direct counting of stained mitotic figures in microdissected crypts.

Results: Median VH was lower in Zambians [283 (262-389) μ m] than black South Africans [412 (235-456) μ m] or white South Africans [377 (285-530)] $p=0.03$, but CD was not significantly different between the groups. Median mitoses/crypt was greater in Zambians [3.7 (1.9-7.9)] than black South Africans [2.4 (0.2-3.7)] or white South Africans compared [2.1 (1-3.7)] $p=0.003$.

Conclusions: We have confirmed the presence of tropical enteropathy in urban black Zambians, and its absence in urban black and white South Africans. Our data suggest that tropical enteropathy is associated with crypt hyperplasia, although this was not accompanied by an increase in crypt depth.

W35

INHIBITION OF CHOLERA TOXIN BUT NOT *E. COLI* ENTEROTOXIN-INDUCED SECRETION BY SUBSTANCE P (SP) ANTAGONIST. Turvill JL, Farthing MJG. DDRC, St Bartholomew's & The Royal London School of Medicine, UK.

Introduction. SP is known to evoke neurally mediated small intestinal fluid secretion in several animal models. Furthermore, SP antagonism inhibits the inflammatory enteritis caused by *C. difficile* toxin A.

Aim. We investigated whether SP mediates the non-inflammatory secretory state induced by cholera toxin (CT) and *Escherichia coli* heat labile (LT) and heat stable enterotoxins (STa) *in vivo*.

Methods. CT and LT experiments: Anaesthetised male Wistar rats (180-220g) were pre-treated with the selective SP antagonist D Pro² D Trp^{7,9} SP (PTT-SP) 3.0mg/kg ip. 20cm small intestinal segments were isolated between cannulae into which 25 μ g CT or 25 μ g LT in 2ml saline was instilled and incubated. After 2h, *in situ* perfusion was performed with plasma electrolyte solution (Na 140, K 4, Cl 104, HCO₃ 40 mmol/l) containing [¹⁴C]-polyethylene glycol as a non-absorbable marker. After an equilibration period, 3x10min collections were made and net fluid and electrolyte movement determined.

STa experiments: After pre-treatment with 3.0mg/kg PTT-SP, the jejunal segment was perfused with PES containing [¹⁴C]-PEG to which 200 μ g/l STa (equivalent to 50000 mouse units) had been added.

Results. CT-induced net water secretion (median -94.0 μ l/min/g dw [IQR -106.5 to -63.0]; n=11) was significantly reduced by pre-treatment with PTT-SP (-10.4 [-42.5 to -4.1]; n=7, $p<0.002$). LT-induced a similar degree of secretion (-67.6 [-89.4 to -33.0]; n=16, $p=0.08$ compared to CT control) which, by contrast, was not inhibited by PTT-SP (-50.7 [-67.6 to -35.3]; n=16, $p=0.3$). In the same way, STa-induced secretion (-65.3 [-83.2 to -54.6], n=6) was not effected by PTT-SP (-77.4 [-81.9 to -76.2]; n=5). Electrolytes paralleled water.

Conclusion. The finding that the SP antagonist PTT SP significantly inhibits CT but not LT or STa-induced secretion is consistent with the observation that there are fundamental differences in the way these three enterotoxins activate a secretory reflex arc in the host.

W34

DETECTION OF INTRALUMINAL SEROTONIN (5-HT) IN PATIENTS WITH HIV-RELATED DIARRHOEA. Kelly P, Turvill JL, Farthing MJG. Digestive Diseases Research Centre, St Bartholomew's & The Royal London School of Medicine & Dentistry, London, UK.

Introduction: The pathogenesis of HIV-related diarrhoea remains unknown and the role of 5-HT as an endogenous secretagogue or prokinetic in this condition is unexplored. Enterochromaffin cells, when activated by enterotoxins, are known to release 5-HT into the intestinal lumen, where it can act as a secretagogue. We investigated whether excess 5-HT is released into the small intestinal lumen in patients with HIV-related diarrhoea.

Methods: Duodenal aspirates were obtained at upper gastrointestinal endoscopy from an unselected group of 69 HIV infected patients with persistent diarrhoea, and from 8 diarrhoea-free control patients being investigated for dyspepsia. Aspirates were collected into protease inhibitors, frozen to -80°C, and 5-HT concentrations determined by HPLC with fluorimetric detection.

Results: 5-HT concentrations were close to the limits of detection in all of the control aspirates (0-0.53nmol/l). 5-HT concentrations were markedly elevated in a sub-group of the patients with HIV related diarrhoea (range 0-224nmol/l). Of the patients with HIV related diarrhoea, 45 (61%) had 5-HT concentrations at control levels, whereas 27 (39%) had markedly elevated concentrations compared to controls ($p=0.04$ by Fisher's exact test). Aspirate pH was not related to 5-HT concentration and some of the higher values were seen in aspirates with pH>7.0. The group of patients with high 5-HT concentrations was not defined by enteric infection, immunoglobulin or soluble tumour necrosis factor concentrations in serum, immunoglobulin concentration in duodenal aspirate, nutritional status or severity of enteropathy.

Conclusion: In a sub-population of patients with HIV-related diarrhoea, intraduodenal concentrations of 5-HT were up to three orders of magnitude higher than in controls. While the clinical relevance of this observation is as yet unclear, similar concentrations have been detected in jejunal perfusates of human volunteers with cholera toxin-induced secretion. These observations raise the possibility that 5-HT may mediate some of the pathophysiological disturbances which underlie this disorder, suggesting novel approaches for therapeutic intervention.

W36

PAROXETINE INHIBITS CHOLERA TOXIN INDUCED SECRETION BY DEPLETING NEURONAL BUT NOT ENTEROCHROMAFFIN (EC) CELL 5-HT. Turvill JL, Farthing MJG. Digestive Disease Research Centre, St Bartholomew's & The Royal London School of Medicine, UK.

Introduction. Depletion of the secretagogue and neurotransmitter, 5-HT, from the small intestine partially inhibits cholera toxin CT-induced secretion. Since a substantial proportion of this secretion is neurally mediated we postulated that a greater anti-secretory effect may result from the selective depletion of neuronal 5-HT from the small intestine. We investigated whether the selective serotonin reuptake inhibitor, paroxetine, would cause neural but not EC cell depletion and whether this would result in the inhibition of CT-induced secretion *in vivo*.

Methods. Two groups of male Wistar rats (180-220g) were gavaged for three days with paroxetine 3mg/kg in 1ml water or water alone, and then anaesthetised. In the first group, the mucosa was gently scraped from the deeper small intestinal layers and 5-HT levels were determined by HPLC with fluorimetric detection. In the second group, 25 μ g CT in 2ml saline was incubated in 20cm small intestinal segments, isolated between cannulae. After 2h, *in situ* perfusion was performed with plasma electrolyte solution (Na 140, K 4, Cl 104, HCO₃ 40mmol/l) containing [¹⁴C]-PEG as a non-absorbable marker, to determine and net water and electrolyte movements. Whole brain was then removed for determination of 5-HT levels as described above.

Results. Mucosal 5-HT levels (med 81.0pmol/mg dw [IQR 65.3 to 85]; n=9) were unaffected by pre-treatment with paroxetine (87.5 [74.3 to 112]; n=6, $p=0.4$ MW). By contrast, brain 5-HT levels (9.4pmol/mg [8.7 to 10.1]; n=8) were significantly reduced by paroxetine (0.9 [0.8 to 1.0]; n=7, $p<0.001$). In keeping with these findings, CT-induced net water secretion (-101.2 μ l/min/g dw [-146.5 to -74.9]; n=14) was inhibited by pre-treatment with paroxetine (-33.2 [-49.5 to -18.6]; n=6, $p<0.0005$). Electrolytes paralleled water.

Summary and conclusion. Paroxetine depletes neuronal 5-HT, as demonstrated by a reduction in brain 5-HT, but not EC cell 5-HT levels within the small intestinal mucosa. We postulate that the associated inhibition of CT-induced secretion results either from (i) the depletion of 5-HT within the myenteric plexus or (ii) the desensitisation of submucosal nerves, which are unable to re-uptake the 5-HT released from activated EC cells.

W37

ISCHAEMIA-REPERFUSION INJURY FOLLOWING SYNGENEIC SMALL BOWEL TRANSPLANTATION INDUCES APOPTOSIS

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Two components cause graft injury following small bowel transplantation; the damage induced by cold ischaemic storage and exacerbation of this following reperfusion. The combined manifestation, termed ischaemia-reperfusion injury, has been described morphologically as causing villous destruction and crypt loss. Many of these cellular changes have been attributed to necrosis.

In a morphological study on syngeneic small bowel transplantation in Lewis rats, grafts were stored in saline (n=6) or University of Wisconsin (UW) solution (n=6) for 24 hours and transplanted with portal venous drainage. Samples of the graft obtained before harvest, after cold ischaemic storage and after 1 hour of reperfusion were processed for light (LM) and electron microscopy (EM) using conventional protocols.

Graft storage resulted in loss of villous integrity (saline worse than UW), but adequate crypt preservation. Apoptosis of some denuded villous epithelial cells was noted; there was no increase in crypt cell apoptosis compared to normal.

After one hour of reperfusion, there was extensive villous destruction. Variable crypt loss was observed, with saline stored grafts showing more damage than UW stored ones. The preserved crypts showed karyorrhectic debris and chromatin margination on LM suggestive of apoptosis, which was confirmed on EM. Some crypt cells exhibited condensation with nuclear and cytoplasmic features of "dark cells". A minor increase in acute inflammatory cells was noted in the lamina propria. Only an occasional crypt cell showed ultrastructural features of necrosis.

This study has identified apoptosis as a prominent mode of cell death following ischaemia-reperfusion injury in transplanted small bowel. This has possible implications on general intestinal ischaemic injury and on the development of specific therapeutic interventions.

W39

ATYPICAL PRESENTATION OF COELIAC DISEASE: A RETROSPECTIVE REVIEW OF ONE INSTITUTION'S EXPERIENCE

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It is known that only a minority of patients with coeliac disease present classically with diarrhoea, steatorrhoea and features of malabsorption; features at presentation are more likely to be red cell abnormalities such as persistent macrocytosis or increased red cell distribution width, weight loss or concurrent associated diseases. In our population the prevalence of coeliac disease is high and often presents atypically.

Clinical and laboratory data were collected from 127 consecutive patients diagnosed histologically with gluten sensitive enteropathy with special reference to the ages at which the patients first developed significant manifestations of the disease, when the disease was diagnosed and the cause of the delay.

70 (50 female) of the 127 patients had a significant delay in diagnosis. Mean age at diagnosis of those diagnosed at initial presentation was 43.6 years (males 45.1, females 42.9); mean age in those whose diagnosis was delayed was significantly higher at 48.5 years (males 48.9, females 48.4, $p < 0.03$); in this group the mean delay was 107.3 months (range 6-480). In 44 patients (33 female) red cell abnormalities only were present; 15 patients had an isolated persistent macrocytosis which resolved on gluten-free diet. 17 patients (9 female) had gastrointestinal symptoms of malabsorption but presented late. 2 patients presented with a concurrent associated disease and 5/50 female patients only had symptoms during pregnancy.

In conclusion, the majority of our patients did not present classically, therefore a high index of suspicion is required to diagnose these patients, especially in patients with refractory red cell abnormalities in populations where the condition has a high prevalence.

W38

INTESTINAL PERMEABILITY AND ABSORPTIVE CAPACITY IN PATENTS RECEIVING PARENTERAL NUTRITION. WS

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Background: It has been suggested that there is a dual supply for enterocyte nutrition, namely luminal during absorption and blood borne during fasting. In rats parenteral nutrition leads to alterations in motility and villus atrophy, but the effect of fasting and parenteral nutrition in man is largely unknown. **Aim:** To assess small intestinal permeability and absorptive capacity in patients requiring parenteral nutrition following prolonged fasting and responses to re-feeding. **Methods:** Weekly assessments of intestinal permeability (lactulose/L-rhamnose) and absorptive capacity (3-0-m-D-glucose, D-xylose, L-rhamnose) were made in 9 patients requiring parenteral nutritional support (for 15 median, range 8-29 days). **Results:** Six of seven patients having been nil by mouth for at least a week had significantly ($p < 0.01$) increased intestinal permeability (differential urinary excretion of lactulose/L-rhamnose 0.18 ± 0.13) as compared with healthy controls (0.03 ± 0.02) and the two who had some oral intake (0.03 ± 0.01). Furthermore absorptive capacity was significantly ($p < 0.05$) impaired in the fasting patients (3-0-m-D-glucose $26.5 \pm 19.5\%$, D-xylose $14.2 \pm 12.2\%$, L-rhamnose $3.7 \pm 2.8\%$) as compared with controls ($44.6 \pm 7.7\%$, $30.7 \pm 7.3\%$ and $10.5 \pm 2.5\%$, respectively). There was a further deterioration in intestinal permeability and absorptive capacity in patients on total parenteral nutrition without oral intake, but not in those concomitantly receiving oral supplementation (500-800 kcal/24 hours). Within a week of re-establishing oral intake intestinal permeability returned towards the reference range (0.066 ± 0.02) and absorptive capacity was restored (3-0-m-D-glucose $48.1 \pm 21.3\%$, D-xylose $26.9 \pm 11.5\%$, L-rhamnose $8.5 \pm 3.9\%$). **Conclusions:** Blood borne nutrition during total fasting is insufficient to maintain gastrointestinal integrity in man which may have implications for microbial translocation and endotoxaemia. As small amounts of food prevent this deterioration every effort should be made to maintain some enteral intake in these patients.

W40

Presentation and Incidence of Coeliac Disease in South Glamorgan. Hawkes N.D, Swift G.L, Davies A, Rhodes J, Smith P.M, Jenkins H.R. (Departments of Child Health & Gastroenterology, University Hospital of Wales, & Department of Gastroenterology, Llandough Hospital, Cardiff.)

Aims: 1) To assess the number of new cases of Coeliac Disease (CD) and Dermatitis Herpetiformis (DH) and the symptoms at presentation in both adults and children between 1st January 1991 and 31st December 1995 for the resident population of South Glamorgan. 2) To compare incidence rates with comparative data for the period 1981-1990.

Methods: All children (aged ≤ 14 years) and adults with CD or DH diagnosed during the study period were identified from hospital activity analysis data, pathology and dietetic records, letters circulated to local General Practitioners and through the local Coeliac Society. All had histologically proven disease and fulfilled the fully revised ESPGAN criteria. The Registrar General's mid year estimates for the population of South Glamorgan were then used to calculate incidences.

Results: A total of 59 new cases of CD were identified (9 children, 50 adults) and 5 cases of DH (all adults). In the children (4 boys, 5 girls) the mean age at diagnosis was 7.6 years (range 1.7- 14.9). 77% presented with abdominal symptoms (with anaemia 57%), none with anaemia alone. Two children presented with failure to thrive and two cases were identified through family screening. In the adults with CD there was a significant difference in the sex ratio (13 males, 37 females) [$p < 0.05$] with a mean age at diagnosis of 50.0 years (range 26.0-88.2, no difference between males and females). 80% presented with abdominal symptoms (with anaemia 48%), 20% with anaemia alone. Of the DH cases 3 were male, 2 female with a mean age at diagnosis of 53.2 years (23.9-74.8). There were two child sibling pairs and two adult patients had a parent with CD.

Table: Annual incidence per 10,000 population. (* $p < 0.001$)

Patient Group	1981-1985	1986-1990	1991-1995
CD-Children	2.08	2.53	2.15
CD-Adults	1.32*	2.15	3.08*
DH	0.43	0.43	0.3

Conclusion: In South Glamorgan the incidence of CD in children and DH in adults has remained constant over the past 15 years however there has been a significant increase in the number of adults diagnosed with CD, the diagnosis being more common in adult women.

W41

COELIAC DISEASE IS ASSOCIATED WITH NON-SMOKING AND CESSATION OF SMOKING.

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The association between ulcerative colitis and non-smoking is well known. Coeliac disease is an allergic mucosal disease which also have an inflammatory component and is associated with inflammatory bowel disease. We investigated patients with coeliac disease to see if they share the same epidemiological characteristic.

Methods: A total of 330 patients with a definitive diagnosis of coeliac disease were prospectively interviewed by a standardised questionnaire. 114 controls were recruited from accident and emergency department and were matched for age and sex.

Results: 37 out of 330 (11.2%) patients with coeliac disease were smokers compared to 48 out of 114 (42%) control patients. This is a significant finding (P< 0.0001; OR:0.174 95% CI 0.105-0.288). There were 90 (27.3%) ex-smokers amongst the coeliac group compared to 3 (2.6%) in the control group. This is also a highly significant finding (P<0.0001; OR:13.88 95% CI 4.30-44.80). 16 of the patients who were ex-smokers stopped smoking after diagnosis of coeliac disease. Exclusion of these patients from the analysis, patients with coeliac disease were still more likely to be ex-smokers compared to controls (P<0.0001; OR 10.70,95% CI 3.30-34.65).

Conclusion: Coeliac disease, like ulcerative colitis is associated with non-smoking, although the relative risk is lower than that quoted for ulcerative colitis. The strikingly large number of ex-smokers amongst coeliac patients is not due to increased medical contact. These findings are unexplained and deserve further study.

W43

INSULIN INDEPENDENCE FOLLOWING COMBINED TOTAL PANCREATECTOMY AND ISLET AUTOTRANSPLANTATION

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Total pancreatectomy is a radical procedure for chronic pancreatitis but renders the patient insulin dependent. Over a 3 year period 14 patients (11 F : 3 M) have undergone total pancreatectomy combined with islet autotransplantation in an attempt to prevent diabetes. Following pancreatectomy islets were immediately isolated using collagenase distension combined with a semi-automated pancreas digestion. In 10 patients islets were also purified on a continuous density gradient. The islets were then transported back to the operating theatre for autotransplantation.

In 12 patients the islets were embolized directly into the liver via the portal vein (median volume 9 mls) in addition 2 of these patients also received islets into the spleen and 2 patients received a splenic autotransplant alone. Post-operative islet autograft insulin secretion was assessed by serum C-peptide levels.

One patient died of a stroke 4 weeks post-operatively. Of the remaining 13 C-peptide levels are available on 12 and are all within the normal range (median 1.29 ng/ml). Four patients developed insulin independence post-operatively but only two patients are currently insulin independent (over 1 year follow-up).

In conclusion insulin independence can be achieved following total pancreatectomy when combined with islet autotransplantation but cannot be predicted by post-operative basal serum C-peptide levels that are within the normal range.

W42

AUDIT OF THE MANAGEMENT OF ACUTE PANCREATITIS IN WESSEX. S.K.C.Toth, S.Phillips, D.Stade, C.D.Johnson. University Surgical Unit, Southampton General Hospital, Southampton SO16 6YD.

In the course of conducting a multicentre trial of a new treatment for acute pancreatitis (AP), prospective data on the management of patients admitted with AP was collected from 8 hospitals in Wessex between Nov.1994-Nov.1995. Recent evidence-based national guidelines for the management of AP have been proposed by the British Society of Gastroenterology. **Aim:**To compare the results of our audit with the proposed audit goals. **Methods:** All patients were seen within 24 hrs of admission and APACHE-II scored. Follow-up data was subsequently obtained through review of the notes after discharge. **Results:**186 patients were admitted with AP: 80 women, 106 men. Age 15-98yr (median 54), aetiology-gallstone(GS)33%, alcohol 20%, other 15%, idiopathic 32%. There were 60 severe cases(32%). The following table summarises the audit findings compared with audit goals:

	Findings (no.)	Audit Goals
Mortality	9.1%(17) (28% severe AP)	<10% (<30%severeAP)
Diagnosis < 48hrs	98.4%(183)	100%
Severity Stratification < 48hrs*	19% (35)	100%
Percentage of Idiopathic Cases	32% (60)	20-25%
Definitive Rx GS in mild AP<4 weeks	33% (15/45)	100%
Severe AP in HDU or ITU	67% (40/60)	100%
Radiological Facilities available (USS, CT, Angiography)	100%	100%
Dynamic CT in severe AP between Day 3 - 10	33% (20/60)	100%
Urgent ERCP in severe GS AP	41% (7/17)	100%

* Using Glasgow, APACHE-II or C-Reactive Protein criteria.

Conclusions:This prospective audit has identified shortcomings in the management of AP. The principal deficiencies were the poor use of objective severity stratification on admission, delayed treatment of gallstones in mild GS AP, and difficulties in providing a 24-hour service for urgent ERCP and bile duct decompression in severe GS AP.

W44

IS PANCREATIC SURGERY SAFE IN A SMALL DISTRICT GENERAL HOSPITAL ?

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It has been suggested that pancreatic surgery should only be performed in larger, specialist units. We reviewed our District General Hospital (DGH) experience over 6 years of 50 consecutive patients (32 males) aged 31-84 yrs(mean 62) undergoing pancreatic surgery. The indications for surgery were pancreatic cancer 25 (50%), acute pancreatitis and its complications 16 (32%), chronic pancreatitis 6 (12%) and others 3 (6%). The procedures performed included; Whipples 12 (24%), Triple bypass 12 (24%), sub-total pancreatectomy 11(including 3 with cyst drainage) (22%), pylorus preserving pancreatoco-duodenectomy 5 (10%), total pancreatectomy 3 (6%), palliative choledocho-jejunostomy 4 (8%) and necrosectomy 3 (6%).

Thirty-day mortality was 6%. Complications included 8 patients with respiratory (2) or cardiac failure (!), pleural effusions (3), arterial bleeding (1) or a bile leak (1); two required re-operation. Median length of hospital stay was 15 days (range 8-77). Median survival for the 27 patients with malignant disease was 8 months (range 1 to 23 months). The 23 patients with benign disease have been followed for a median of 3 years; 3 have died, one from recurrent acute pancreatitis and two others from unrelated causes. Of the 20 surviving,4 have developed pancreatic insufficiency and a further 2 have recurrent pain.

We conclude that successful pancreatic surgery can be performed safely in a DGH setting. Patient selection and expertise are more important than numbers.

W45

DIFFERENCES IN PERCEPTION OF QUALITY OF LIFE ISSUES BETWEEN PANCREATIC CANCER PATIENTS AND HEALTH PROFESSIONALS.

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Despite advances in medical and surgical interventions the outlook for the pancreatic cancer patient remains gloomy. Recently, attention has focused on the quality of life (QOL) of such patients. Yet little research has been undertaken and no disease specific QOL questionnaire exists. During development of a pancreatic cancer module to supplement the European Organisation for Research and Treatment of Cancer (EORTC) core cancer questionnaire, the QLQ-C30, we have noted differences in perception between health professionals and patients.

Methods: We used guidelines published by the EORTC QOL study group. An extensive literature review was performed to identify relevant issues. 40 pancreatic cancer patients and 18 health professionals have been asked to identify the most important and relevant QOL issues. Of these, 21 patients and 6 health professionals were interviewed to gain insight into why such issues were important in pancreatic cancer. Interviews were semi-structured and were analysed using a grounded theory approach.

Results: The literature review was largely unproductive. The content of data gathered from professionals and patients were similar. A list of 42 relevant and specific issues was generated suitable for inclusion in a pancreatic cancer module. These included specific symptoms such as pruritus, jaundice, indigestion and abdominal pain as well as additional QOL issues related to fear of future, body image and support. However, the context in which these issues were identified differed between the two groups. Health professionals took a mechanistic approach and perceived a direct relationship between severity of symptoms and overall QOL, whereas patient's perception related to the need to introduce or alter existing coping strategies. The success or otherwise of these coping strategies influenced QOL perception.

Conclusion: Many QOL instruments are designed from the viewpoint of the health professional. This work demonstrates the importance of a qualitative patient centred approach to initial development. Patient's perceptions should be included in all stages of QOL instrument development. A 27 item module has now been constructed, refined and approved by the EORTC for multi-lingual pretesting and field-testing.

W47

THE PAROTID GLANDS ARE NOT VULNERABLE TO FACTORS RESPONSIBLE FOR CHRONIC PANCREATITIS

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BACKGROUND: The parotid glands share many functional and morphological characteristics with the pancreas, suggesting they may also be vulnerable to factors responsible for alcoholic and idiopathic chronic pancreatitis (ACP and ICP). Previous studies have investigated this potential association by measuring changes in salivary composition or antibodies against salivary gland antigens in CP and reached differing conclusions. The aim of the present study was to test this hypothesis directly by determining the prevalence of parotid gland abnormalities in patients with CP by ultrasonography. This technique is sensitive in detecting parotid duct ectasia and the presence of intraductal stones and glandular calcifications.

METHODS: The parotid glands of 23 patients with CP diagnosed on the basis of abnormal ERPs (suspected aetiologies: alcohol; n=9, idiopathic; n=7, gallstones; n=7) together with 15 total controls were scanned using a linear sector 7.5 MHz probe on a ATL HDI 3000 scanner. All machine parameters were set for optimal scanning at glandular depth. A search was made for major (Stensen's duct) and minor ductal ectasia and calcification.

RESULTS: Stensen's duct was visualised in all control subjects, measuring 0.5 - 1 mm in diameter. There was no difference in duct diameter between controls and patients with CP. Similarly, ultrasonography did not detect any duct ectasia or glandular calcification in either the controls or any of the patients with pancreatitis.

CONCLUSIONS: According to the parameters assessed, parotid gland morphology in patients with ACP and IPC is unchanged compared to that of controls and patients with gall stone CP. This suggests that development of ACP and ICP depends on factors particular to the pancreas, rather than on any antigenic or metabolic characteristic it may share with the parotid.

W46

LEXIPAFANT, A PLATELET ACTIVATION FACTOR(PAF) ANTAGONIST, REDUCES MORTALITY IN A RANDOMISED PLACEBO-CONTROLLED STUDY IN PATIENTS WITH SEVERE ACUTE PANCREATITIS.

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The complications and early deaths associated with acute pancreatitis appear to involve inappropriate immune system activation. PAF is a central mediator of this response. Our aim was to investigate the effect of lexipafant, a potent PAF antagonist, in a randomised, double-blind, placebo-controlled study, in patients predicted to develop complications.

Patients with acute pancreatitis and APACHE II score >6 were randomised within 72hrs of onset of symptoms to receive an infusion of lexipafant (100mg/day for 7 days) (n=139) or identical placebo (n=151). Seven patients who died were excluded (wrong diagnosis, n=3; unrelated cause of death, n=3; protocol violation (cancer of pancreas), n=1). Overall and attributable mortalities were not significantly less after lexipafant (n=18, 12%) and (n=14, 9%) than after placebo (n=24, 17%) and (n=21, 15%); (0.1 < p < 0.2). However, 11 (10%) of 107 patients treated within 48hrs of onset died, significantly less than 20 (20%) of 98 given placebo within 48hrs (p=0.04). Attributable mortality in these patients was significantly less with active treatment (8 of 104, 8%) than placebo (17 of 95, 18%); (p=0.03). Median change in organ failure score on day 3 was significantly different in the two groups (lexipafant -1 (-1 to 0), placebo 0 (-1 to 0); p=0.04) and there were fewer local complications in the lexipafant group (30/148, 20% vs 41/138, 30%; p=0.065).

Lexipafant appears to reduce complications and death in patients predicted to have severe pancreatitis. This effect is most marked in patients treated within 48 hrs of onset of symptoms, consistent with the supposed mode of action of the drug.

Liver W48-W72

W48

ONDANSETRON IN THE TREATMENT OF THE PRURITUS OF CHOLESTASIS: A RANDOMISED CONTROLLED TRIAL.

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Conventional drug treatment of the pruritus of cholestasis may be unsuccessful. Serotonin receptors on dermal sensory nerve-endings may play a role in the perception of pruritus, and case reports have suggested benefit from the 5-HT₂ receptor antagonist, ondansetron. **Aim.** To define the efficacy of ondansetron in the pruritus of cholestasis. **Patients.** 19 patients (16 female, median age 59 y) were enrolled (17 PBC, one chronic rejection post orthotopic liver transplantation, one hepatitis C). All had pruritus resistant to treatment with cholestyramine, ursodiol (each five patients), antihistamines (4), tamoxifen (2), cyclosporin-A and rifampicin. Anti-pruritic medications were stopped 3 days before study entry. **Methods.** Perception of itch was recorded (hourly by day) using a visual analogue score (VAS), and scratching activity (SA) (independent of limb movements) measured by means of a piezo-electric crystal attached to the nail. Both were recorded for 24 hours pre- and post-treatment and the VAS was continued for one week. Patients were randomised, double-blind, to receive either ondansetron or placebo. A single intravenous bolus of 8mg ondansetron / placebo was followed by oral ondansetron 8mg / placebo twice daily for five days. Meaningful relief was defined as reduction to <50% of baseline pruritus on day 1. **Results.** Treatment and placebo groups were well-matched for age, sex, diagnosis, severity of liver disease, previous anti-pruritic medication and baseline pruritus burden and SA. Pruritus showed diurnal variation, with evening exacerbation. Pruritus burden (the area under the curve of VAS v time) was reduced on the first treatment day compared to baseline in both ondansetron and placebo groups (p < 0.05) but there were no significant differences at any time-point between the groups in pruritus burden, SA or in the time to meaningful relief. **Summary.** Ondansetron has no advantage over placebo in the treatment of the pruritus of cholestasis.

W49

JAUNDICE ASSOCIATED WITH AUGMENTIN: THE TIP OF THE ICEBERG? ¹J.W. O'Donoghue, ²K. Oien, R. C. Brown, P. Bramley, K. M. Cochran, R.W. Crofton, W.S. Hislop, R. Park, ³R.N.M. MacSween, ⁴P. R. Mills. Depts. of ¹Gastroenterology and ²Pathology, Western Infirmary, Glasgow and West of Scotland Hospitals

Augmentin (amoxicillin and clavulanic acid) is among the most commonly prescribed antibiotics worldwide. Cholestasis associated with Augmentin in the absence of other known cause was first recognised in 1988. **Aims.** To estimate the incidence, patient profile and outcome of Augmentin-associated cholestasis in the West of Scotland (pop. 2.5m) from 1992-1996. **Case finding methods.** Direct postal questioning of 23 gastroenterologists in the West of Scotland, search of coded discharge diagnoses in the Glasgow area, and search of pathology records (K.O.) **Results.** 19 cases of jaundice were identified (ten male, mean age 57.8y, range 44-91y). Full clinical details were available in 15 patients. In no patient was a causative link with the drug suspected at time of referral. Duct dilatation was excluded by ultrasound and hepatitis serology was negative in all patients. Median interval between start of drug therapy and development of jaundice was 14.5d (range 6-46d). Median peak bilirubin was 226 μ mol/l (range 129-598 μ mol/l). One death occurred, from unrelated causes, in a 91yo patient who had mild, resolving jaundice. Cholestasis resolved after median 93d (range 35-186d) in all but one patient, in whom a mild transaminitis has persisted for 4 years. Duration of jaundice correlated with the length of interval between drug exposure and onset of jaundice ($r=0.76$), but not to age, sex, dose or duration of treatment. The implied frequency in the West of Scotland in 1996 was one case of cholestasis per 22,000 Augmentin prescriptions. Liver biopsy, performed in eight patients, showed portal tract chronic inflammation, cholestasis, eosinophilia and varying degrees of cholangiopathy in all cases. Granulomatous inflammation was present in one. **Conclusions.** Jaundice associated with Augmentin is increasingly recognised, may be severe and prolonged, and is frequently delayed after drug exposure which may hinder diagnosis. Complete recovery is usual.

W51

LIVER FUNCTION TESTS AND LIVER DAMAGE IN HAEMOCHROMATOSIS. D K George, D H C Crawford and L W Powell (introduced by R I Russell). The Liver Unit, Queensland Institute of Medical Research, Brisbane, 4029, Australia.

Haemochromatosis (HC) is an inherited disorder of iron metabolism which can cause hepatic cirrhosis. The prevalence in most Caucasian populations studied is approximately 1 in 300 though the disorder remains under diagnosed. One reason for such under diagnosis may be that liver function tests (LFT) are often normal. The significance of abnormal LFT in HC has not previously been studied.

50 HC patients were analysed with respect to abnormalities of transaminases at diagnosis, age, sex, transferrin saturation, serum ferritin, hepatic iron concentration (HIC), Scheuer grade of fibrosis and the presence of other histological hepatic features.

56% had normal LFT at diagnosis compared to 44% with abnormal LFT. There were no significant differences between the two groups in terms of age, transferrin saturation or HIC. The group with abnormal LFT however had significantly higher serum ferritin levels (1812 \pm 986 vs 669 \pm 407, $p<0.0001$) and a greater male preponderance ($p<0.05$). 29% of patients with normal LFT had no histological abnormalities other than increased iron stores. 35% of patients with normal LFT had hepatic fibrosis without histological inflammation, steatosis or other histological abnormalities. All patients with abnormal LFT had histological abnormalities other than increased hepatic iron stores. Patients with abnormal LFT were more likely to have fibrosis than those with normal LFT (82% vs 54%, $p<0.05$) and to have a more severe grade of fibrosis (1.9 \pm 1.4 vs 0.8 \pm 0.8, $p<0.001$).

Liver damage can develop in HC due to increased iron stores alone and in the presence of normal LFT. However, HC patients with abnormal LFT are more likely to have fibrosis and at a more advanced stage. Therefore, although abnormal LFT indicate the presence of hepatic complications in haemochromatosis, normal LFT do not preclude the presence of hepatic damage. Recently the HC gene has been cloned and a genetic diagnostic test may soon be available. However, in general liver biopsy is still indicated in haemochromatosis for diagnosis and assessment of hepatic complications.

W50

FINDINGS ON LIVER BIOPSY FOR ABNORMAL LIVER FUNCTION TESTS IN THE POST HEPATITIS C TESTING ERA.

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Background. Abnormal liver function tests are relatively common but their significance in the presence of negative serological tests is uncertain.

Methods. We have prospectively studied 210 consecutive patients aged 18 to 78 undergoing investigation for abnormal liver function tests, defined as persistent elevation of ALT or GGT over 6 months, in whom serology for hepatitis B and C, autoantibodies, serum ferritin, alpha-1-antitrypsin, copper studies (where appropriate), and ultrasound scanning were normal/negative. Alcohol histories were taken from patients and corroborating relatives and if consumption >4g per day patients were excluded.

Results. 8 patients refused liver biopsy. 9/202 (4.5%) were cirrhotic on biopsy and a further 19 (9.4%) had increased fibrosis. Final diagnoses were Non-Alcoholic steatohepatitis 68 [34%], fatty liver without inflammation 74 [37%], alcohol related liver disease 6 [3%], autoimmune hepatitis (steroid responsive) 4 [2%], drug induced 31 [15%], primary biliary cirrhosis 1 [0.5%], haemochromatosis 2 [1%], amyloidosis 1 [0.5%] and normal liver 15 [7.5%]. Complications of liver biopsy (non U/S guided, menghini needle) were 4 patients with post biopsy pain and one with a bile leak requiring 6 days hospitalisation. No patients suffered haemorrhage.

Conclusions. Liver biopsy for abnormal liver function tests produces a diagnosis of potentially progressive liver disease in 55%. 13% of patients had significant fibrosis or cirrhosis at the time of biopsy. Clinical management was altered in 43 patients (21%) and only one significant complication of liver biopsy was seen. Patients with persistent abnormalities of their liver function tests should be offered liver biopsy.

W52

THE EFFECT OF HORMONE REPLACEMENT THERAPY ON SERUM AND URINARY MARKERS OF BONE TURNOVER IN PRIMARY BILIARY CIRRHOSIS. SP Pereira¹, J O'Donoghue¹, C Moniz², C Mackintosh², H Abrahams², M Buxton-Thomas³, Roger Williams¹.

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Evidence from retrospective studies suggests that hormone replacement therapy (HRT) is well-tolerated and may be helpful in retarding the rate of bone loss in primary biliary cirrhosis (PBC). However, there have been no prospective studies in PBC of the effect of HRT on bone mineral density or serum and urinary markers of bone turnover. **Methods:** 42 post-menopausal women with PBC (median age 57 yr, range 52-63 yr) were treated with calcium+vitamin D, either alone (n=22) or together with topical HRT (n=20; Estracombi, Ciba). Bone densitometry (Lunar) of the femoral neck and L2-L4 vertebrae was performed at baseline, and serum and urinary markers of bone turnover measured at three-monthly intervals. We report here our baseline and three-month findings. **Results:** The two groups were well-matched for age, year of menopause (49 yr, 43-51 yr), histological stage, serum bilirubin level (median 15 μ M, range 4-65 μ M) and bone densitometry scores. In the 42 patients, spinal or femoral osteopaenia (T score -1 to -2.5) was present in 16 (38%), while 7 others (17%) had established osteoporosis (T < -2.5). Baseline serum osteocalcin and adjusted calcium concentrations were 7.0 μ g/l (4.2-14.9 μ g/l) and 2.4 mM (2.2-2.6 mM), respectively, which did not change significantly at three months in either group. In the controls, urinary calcium and creatinine levels, and urinary deoxyypyridinoline:creatinine ratios, were similar at baseline and three months. In contrast, urinary calcium concentrations fell significantly in the HRT group, from 2.5 mM to 1.2 mM ($p<0.05$). Overall, HRT was well-tolerated, with no increase in cholestasis and only one withdrawal due to minor side-effects. **Conclusions:** The initial results of this prospective study confirm that osteoporosis is common in post-menopausal women with PBC, and that topical HRT is well-tolerated. Compared with calcium+vitamin D alone, supplemental HRT is associated with decreased urinary calcium excretion -- a sensitive marker of bone turnover.

W53

**IgG, IgM, IgA HEAT SHOCK PROTEIN ANTIBODIES
IN PRIMARY BILIARY CIRRHOSIS-
EFFECT OF UDCA THERAPY**

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Primary biliary cirrhosis (PBC) is an autoimmune disease which results in destruction of intrahepatic bile ductules. Epitopes shared by an infectious agent and the host have been proposed as a possible link between infection and autoimmunity. Heat shock proteins (HSP) are produced by prokaryotic and eukaryotic cells in response to stress. Expression of HSP on bile duct epithelium has been demonstrated, and $\gamma\delta$ T cells (capable of mounting an immune response to HSP) found in the liver may play a role in the destruction of bile ducts. Ursodeoxycholic acid (UDCA), the treatment of choice in PBC, has immunomodulatory effects. We hypothesize that antibodies to HSP are involved in the pathogenesis of PBC, and that UDCA treatment modifies this response. **Aims:** To determine the presence of HSP antibodies in PBC and to assess the effect of UDCA treatment. **Methods:** IgG, IgM and IgA antibodies to the 65kD HSP were assessed in 41 PBC patients (F:M 39:3, median age 65 years range 33-82), using an in house ELISA. 33 were studied after a median of 2 months of UDCA (10-15mg/kg/day). 45 normal controls (F:M 35:10, median age 55 range 30-65) were also studied. **Results:** The log optical density - log mean of normals (\pm SEM) of the controls and PBC group are shown below.

	Normals n=45	All PBC n=41	Early PBC n=27	Late PBC n=14
IgG	-0.006 \pm 0.011	0.044 \pm 0.012*	0.050 \pm 0.016*	0.032 \pm 0.018
IgM	-0.005 \pm 0.010	0.065 \pm 0.015*	0.035 \pm 0.014*	0.124 \pm 0.029* Φ
IgA	-0.001 \pm 0.005	0.055 \pm 0.006*	0.053 \pm 0.007*	0.057 \pm 0.010*

* $p < 0.02$ compared with normal controls $\Phi p < 0.03$ vs early PBC

UDCA treatment did not alter HSP antibody levels in any stage of PBC for all classes of Ig. **Conclusion:** Antibodies to HSP are elevated in PBC. Short term UDCA therapy does not affect this response. The presence of antibodies to HSP may suggest a role for this protein in the pathogenesis of PBC. Further studies to define their role in the pathogenesis and as possible markers of disease activity with longer treatment with UDCA are needed.

W55

**BCL-2 AND WAF PROTEIN EXPRESSION IN
CHRONIC LIVER DISEASE**

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Apoptosis is a possible mechanism of cell death in liver disease. Its role has not been adequately studied. Apoptosis is controlled by several genes whose protein products either inhibit or accelerate apoptosis.

We therefore studied the protein expression of one inhibiting gene (bcl-2) and one promoting gene (waf).

Liver biopsies from 10 patients with primary biliary cirrhosis (PBC), 10 with chronic hepatitis B, and 10 with chronic hepatitis C, were studied by immunocytochemistry using monoclonal antibodies against bcl-2 and waf proteins.

Bcl-2 was expressed in bile ductular cells of all patients studied, but in PBC it was either overexpressed or not expressed in most intrahepatic bile ductules.

There was profound infiltration of portal tracts by bcl-2 positive lymphocytes in PBC and to a lesser extent in chronic hepatitis. Moreover many positive intralobular lymphocytes were identified. By contrast waf protein expression was identified in nuclei of hepatocytes near areas of piecemeal necrosis only in chronic hepatitis either B or C. In PBC no positive nuclei were noted.

Conclusions: 1) Apoptosis controlling proteins are expressed in liver disease. 2) Clones of apoptosis resistant infiltrating lymphocytes expressing bcl-2 are predominant in chronic liver disease.

3) Apoptosis promoting proteins are expressed in hepatocyte nuclei in viral hepatitis but not in PBC.

W54

**URSODEOXYCHOLIC ACID THERAPY FOR PRIMARY BILIARY
CIRRHOSIS: 10 YEARS' POPULATION-BASED EXPERIENCE.**

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From 1981 all symptomatic cases of primary biliary cirrhosis (PBC) in a health district of 153,000 residents have been identified by the local gastroenterologist and liver biopsy performed in all but one. After April 1987 all cases seen were offered treatment with ursodeoxycholic acid (UDCA) 750 mg daily. The 37 treated with UDCA were followed up at 1, 2, 4, 6, 9, & 12 months and then 6 monthly. Results were compared with historical local controls and published data in other series.

There was a uniform early improvement in abnormal "liver function" tests, maximal at 4 months. There was an early improvement in histology in 3 out of 8 rebiopsied at 4 months. Twenty-eight patients reported improvement or cure in symptoms, 7 had no change, and in 2 patients there was a prompt exacerbation which led to immediate cessation of treatment.

Overall survival was significantly improved, though it was still less than the general population and the effect was only seen after 2 years' treatment. Histological stage I disease, lower age and lower initial bilirubin, and to a lesser extent serum IgG and haemoglobin levels predicted better survival. In stage I disease median follow-up was 4 years. Survival was normal in the 14 allocated to UDCA, and 1 case followed for 7 years lost all clinical evidence of disease and may have been cured. In stage II to IV disease median follow-up was 2½ years: in the 23 allocated to UDCA there was a sustained trend to improved survival (37% v. 28% at 7 years, Kaplan-Meier analysis). Most deaths related to liver disease and by chance none of the patients has proceeded to liver transplant, so these are true absolute life tables.

CONCLUSION - UDCA is effective and easy to use, avoids the need for more toxic drugs in PBC, and should be offered to all cases not imminently expecting transplant. There may be a case for treating pre-symptomatic disease.

W56

**NITRIC OXIDE RELEASE IN THE SPLANCHNIC CIRCULATION
OF CIRRHOTIC RATS**

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Enhanced splanchnic vascular nitric oxide (NO) activity has been implicated in the pathogenesis of portal hypertension associated with cirrhosis of the liver. However, the portal venous concentration of total nitrite and nitrate (nitric oxide metabolites, NOx), which is established as a reliable indicator of NO production, has not been previously studied.

Experimental micro-nodular cirrhosis was induced in adult male Wistar rats by the administration of phenobarbitone and carbon tetrachloride (n=7). Age- and weight-matched rats (n=5) and phenobarbitone treated rats (n=5) served as controls. We assayed portal venous concentrations of NOx and total biochemical activity of nitric oxide synthase (NOS) in the liver and mesentery of both groups.

Cirrhotic rats had significantly higher mean portal pressure than controls {11.00 (S.E.M. 1.22) vs. 4.80 (0.96) mmHg; $P=0.002$ }. Portal venous concentrations of NOx were significantly lower in cirrhosis than in controls {75.33 (16.54) vs. 128.34 (15.66) $\mu\text{mol.l}^{-1}$; $P=0.02$ }. There was a significant negative correlation between portal pressure and portal venous NOx concentrations { $r=-0.57$; $P=0.04$ }. Total NOS activity in the mesentery was higher in cirrhosis than controls {6.17 (1.19) vs. 3.30 (0.68) $\text{pmol.g}^{-1}.\text{min}^{-1}$; $P=0.04$ }. In contrast, hepatic total NOS activity was similar in both groups {11.79 (2.14) vs. 10.06 (1.42) $\text{pmol.g}^{-1}.\text{min}^{-1}$; $P=0.60$ }.
 $P=0.60$.

These results imply that total NO release in the portal venous drainage territory of cirrhotic rats is decreased, although mesenteric NOS activity is enhanced. We speculate that NO release in the splanchnic viscera may be downregulated in response to the overactivity of another putative vasodilator which is NO-independent. The inverse relationship between portal pressure and portal venous NOx concentration would support this hypothesis.

W57

EFFECT OF TIPSS ON RENAL BLOOD FLOW IN CIRRHOTIC PATIENTS.

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It has been suggested that an acute increase in portal pressure can cause an immediate reduction in renal blood flow (RBF) via an hepato-renal reflex. In addition, transjugular intrahepatic portosystemic stent-shunt (TIPSS) can improve renal function by mechanisms that remain unclear. We used TIPSS placement as a model to investigate the effect of an acute reduction in portal pressure on RBF and other haemodynamic parameters.

Methods: 10 cirrhotic patients (8 alcohol related; 6 male; mean age 59.5(4.6) yrs; mean CPS 8.3(1.1)) were studied during elective TIPSS procedure (8 for variceal haemorrhage, 2 for refractory ascites). Unilateral RBF (thermodilution method) was measured prior to and at 5, 15, 30, 45 and 60 minutes after shunt placement. Right heart catheterization was undertaken prior to and 30 minutes following shunt placement to measure cardiac output (CO), systemic vascular resistance (SVR) and mean pulmonary artery pressure (PAP). Heart rate (HR), mean arterial pressure (MAP) and right atrial pressure (RAP) were also measured at these times.

Results: See table. No change was observed in RBF at any time point after TIPSS. Porto-atrial pressure gradient fell by a mean of 16.7(1.6)mmHg ($p<0.001$). RAP rose from 2.0(1.2) to 8.4(1.2)mmHg ($p<0.001$), but no change was seen in HR or MAP.

	RBF (ml/min)	CO (l/min)	SVR (DS/cm)	PAP (mmHg)
pre-TIPSS	252.1(66.8)	5.8(1.0)	1313.5(111.8)	13.1(2.1)
+ 30 mins	277.2(69.0)	7.5(1.1)	932.8(111.6)	25.2(2.0)
p value	NS	$p<0.005$	$p<0.005$	$p<0.001$

Conclusion: There is no acute increase in RBF in response to the acute drop in portal pressure caused by TIPSS. Any improvement in renal function following TIPSS does not appear to involve an immediate increase in RBF.

W59

A NEW AUTOANTIGEN IN AUTOIMMUNE LIVER DISEASE: ARGININOSUCCINATE LYASEPelli N¹, Cançado E¹, Mieli-Vergani G², Vergani D¹. Institute of Hepatology¹, University College London Medical School, London; Depts of Child Health, King's College Hospital², London

Autoantibodies have a central role in the diagnosis and classification of autoimmune liver diseases (AILD). LC1 antibody (LC1-ab), a second marker of a severe form of autoimmune hepatitis (AIH), is often associated with LKM-1 and is detected by immunofluorescence (IFL), double dimension immunodiffusion (DDI) and Western blotting (Wb). Ultracentrifugation and immunofluorescence studies show the LC1 antigen to be present in the cytosol of periportal hepatocytes, its molecular nature remaining unknown. To investigate the target of LC1-ab, we have used two LC1-ab +ve sera (one ANA and one LKM-1+ve) to screen a panel of 18 periportal enzymes by DDI. These enzymes, with a median degree of homology with the human counterpart of 78%, included: lactic dehydrogenase, arginase, argininosuccinate lyase (ASL), beta-glucuronidase, malic enzyme, pyruvate kinase, fructose-1,6-diphosphatase, alcohol dehydrogenase, 6-phosphogluconic dehydrogenase, malic dehydrogenase, hexokinase, cytochrome oxidase, aspartateamino transferase, alanineamino transferase, adenosine-5-triphosphatase, gamma-glutamyl-transpeptidase, glutathione peroxidase and alkaline phosphatase. Both sera recognised ASL, a cytosolic enzyme involved in the urea cycle and gave a line of complete identity between themselves. ASL and LC1 antibodies were tested in 120 patients, age range 1-77 years (median 20), 74 with AILD (25 AIH type I, 32 AIH type II, 17 PBC), 15 chronic HBV infection, 13 α 1 anti-trypsin deficiency, 18 extrahepatic autoimmune disorders (16 connective tissue disease, 1 autoimmune thyroiditis, 1 autoimmune haemolytic anaemia) and 24 healthy controls, age range 5-20 years (median 15). Thirteen were positive for ASL: 2 AIH type I (8%), 7 AIH type II (22%) and 4 PBC (23%). All other patients and healthy controls were negative. There was no correlation between ASL and LC1 positivity.

AILD n° of	LC1-ab+ve	ASL-ab+ve	LC1 and ASL-ab+ve
74	15 (20%)	13 (17%)	4 (5%)

Under high resolution DDI conditions (0.8% Agarose and 3% PEG), using the two LC1-ab reference sera and testing simultaneously each serum against ASL and LC1 substrates, two lines were formed against LC1, one of which was of partial identity and the other of non identity with ASL. In conclusion a new autoantigen -ASL- is present in AILD. The molecular nature of LC1 remains still to be defined.

W58

A PROSPECTIVE STUDY OF SPEEDBAND VERSUS STEIGMANN-GOFF IN ENDOSCOPIC LIGATION OF OESOPHAGEAL VARICES.

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Endoscopic ligation is the treatment of choice for oesophageal variceal obliteration; however the use of an overtube leads to significant morbidity and mortality. Recent advances in endoscopic technology have led to development of multiple banding devices that do not require the application of an overtube. In the present study we prospectively examined the safety and efficacy of one such device: Speedband against the conventional Stiegmann-Goff (Bard) ligator.

Patients and Methods. We prospectively studied 99 variceal banding sessions in 45 patients. Speedband ligation was performed in 60 sessions, and Bard in 39 sessions. Parameters examined included sedation dosage, patient discomfort (mild, moderate, or severe), upper oesophageal damage, immediate band slippage, total time of banding session, total time required for band application (first to last band), and average time of application per band. Variceal ligation sessions were randomly assigned to one of the 4 endoscopists experienced in both methods of band application, and the Olympus Q200 endoscope was used for all procedures.

Results. Patients were well matched at time of endoscopy with respect to number of varices (mean 3.3 vs 3.4), grade of varices (1.8 vs 1.7), age (49 yrs vs 50.4 yrs), number of bands applied (4.0 vs 3.4), and Child's-Pugh score (64% vs 68% Child's-Pugh A), Speedband vs Bard respectively. The use of Speedband was associated with a significant reduction in midazolam (7.3 mg vs 9.2 mg, $p=0.03$), and pethidine (10.4 mg vs 24.3 mg $p=0.01$) requirements. Patients undergoing Speedband application experienced less discomfort (90% vs 66% mild discomfort, $p<0.001$), and less upper oesophageal damage (76% no damage vs 55%, $p<0.01$). One patient undergoing Bard ligation died due to an oesophageal rupture from the overtube, and in a further 2 cases ligation was abandoned due to oesophageal haemorrhage; no such complications occurred in the Speedband group. The total time of the endoscopic session was reduced in the Speedband group (7 min 58 secs vs 11 min 33 sec, $p<0.001$), as was the time required for band application (2 min 52 secs vs 5 min 9 secs, $p<0.001$), and average time taken per band application (46 secs vs 1 min 32 secs, $p<0.01$). There were no differences between the groups with respect to immediate band slippage (18% vs 33%, $p=0.09$).

Conclusions Speedband ligation is safer, quicker, and associated with less patient discomfort and morbidity when compared with Bard ligation. On the basis of this data, a multiple banding device is the method of choice for endoscopic variceal ligation.

W60

Detection of anti conformational CYP2D6 antibodies in patients with autoimmune liver disease and HCV infection using a novel radioligand assay

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LKM-1 antibody is the diagnostic marker of autoimmune hepatitis (AIH) type 2 and is also found in a proportion of patients with hepatitis C virus (HCV) infection. Cytochrome P4502D6 (CYP2D6) is a major target antigen of LKM-1 in AIH, since the majority of LKM-1 positive AIH sera recognise the prokaryotically expressed cytochrome. In contrast, only a minority of LKM-1/anti-HCV positive sera do so. In order to investigate the target of LKM-1 in HCV infection, we have established a highly sensitive and specific radioligand assay using eukariotically expressed CYP2D6 as target. A 1.2 kb human CYP2D6 cDNA was isolated from a human liver cDNA library and subcloned into an *in vitro* transcription vector pSP64 Poly(A). Recombinant CYP2D6 protein was then produced using an *in vitro* transcription/translation and metabolically labelled with ³⁵S methionine. This served as target in the immunoprecipitation assay. Antibodies that bound radiolabelled CYP2D6 were immunoprecipitated using protien A-Sepharose beads and their levels assessed as cpm in a liquid scintillation analyzer. A total of 53 LKM-1 positive sera from 22 children with AIH (median age 10, range 1 to 20 yrs) and 31 adults with HCV infection (median age 49, range 16 to 71 yrs) were tested. One hundred and twenty five LKM-1 negative sera from 101 age matched children with liver disease (9 HCV infection, 23 HBV infection, 19 AIH type 1, 18 autoimmune sclerosing cholangitis, 19 α 1-antitrypsin deficiency and 13 Wilson's disease) and 24 adults with systemic lupus erythematosus and sera from 37 healthy children and 20 adults were also tested. Amongst LKM-1 positive sera, reactivity to ³⁵S labelled CYP2D6 was observed in all sera from AIH and in 26 (84%) from HCV infection. The cpm in both conditions were significantly higher than in normal controls ($P<0.0001$), and were correlated with the immunofluorescence titres of LKM-1 in AIH ($r=0.84$, $P<0.001$) but not in HCV infection ($r=0.26$). No reactivity to ³⁵S labelled CYP2D6 was observed in patients negative for LKM-1 and in normal controls. In conclusion: a) CYP2D6 is a major target antigen in both AIH and HCV infection but the antibody affinity is different; b) the novel radioligand assay is highly sensitive and specific.

W61

THE IMPACT OF CHRONIC HEPATITIS C INFECTION ON HIV DISEASE AND PROGRESSION IN INTRAVENOUS DRUG ABUSERS. GH Haydon¹, CS Blair¹, PJ Flegg², RP Brettie², SM Burns³, PC Hayes¹. Departments of Medicine¹ and Infectious Diseases², University of Edinburgh and Regional Virus Laboratory³, City Hospital, Edinburgh.

It is unclear whether co-infection with hepatitis C virus (HCV) can influence HIV related morbidity or mortality, either by accelerating HIV-related disease progression, or by contributing to end stage liver disease. The aim of this study was to examine the effect of HCV infection on the severity and progression of HIV disease in a cohort of Edinburgh IVDA's. **Methods:** In 240 (47%) out of 508 patients in the Edinburgh IVDA cohort, HIV seroconversion dates (midpoint between last negative and first positive test) and anti-HCV serology were available. Comparison of the anti-HCV positive and anti-HCV negative groups was performed by Chi-square analysis; progression from date of HIV seroconversion was calculated by Kaplan-Meier survival analysis. Parameters assessed included clinical end points (time of development of significant symptoms attributable to HIV (CDC stage IV), time of development of AIDS (CDC 1993 criteria), and time of death) and immunological end points (time of CD4⁺ counts dropping below 200/mm³, 100/mm³ and 50/mm³ respectively).

Results: 202 out of 240 patients (84%) had positive anti-HCV serology. There was no significant difference in the frequency of clinical and immunological end points between the anti-HCV positive and negative groups. Progression analysis from HIV seroconversion to HIV related clinical endpoints indicated that anti-HCV serology was not a significant factor influencing the rate of HIV progression (relative risks (RR) for anti-HCV positive group: seroconversion to CDC IV: 1.01; seroconversion to AIDS: 1.05; seroconversion to death: 0.90). Likewise HCV serostatus did not significantly affect progression to immunological end points (RR for anti-HCV positive group: seroconversion to CD4+<200: 1.04; seroconversion to CD4+<100: 1.13; seroconversion to CD4+<50: 0.97). **Conclusions:** This study demonstrates that HCV coinfection does not influence the rate of progression to either clinical or immunological end points in our population of HIV-infected drug users. Further data are required to assess the effect of HIV on the progression of HCV-related liver disease.

W63

LOWER PREVALENCE OF MARKERS OF AUTOIMMUNITY IN CHRONIC HEPATITIS C IN NORTH-EAST OF ENGLAND. F.Zappala¹, MF Bassendine.

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Background: It has been suggested that there is an interaction between HCV and autoimmunity, in some case series of chronic hepatitis C high overall prevalence of serum antitissue antibodies (41-66%) and rheumatoid factor (70-76%) have been reported. **Aim:** to estimate the prevalence of markers of autoimmunity in pts affected by chronic hepatitis C living in the North-East of England. **Patients and methods:** 101 antiHCV+ve pts by second-generation ELISA or RIBA (59 male, 42 female, mean age 43±10, range 24-88) with chronic hepatitis C diagnosed on the basis of persistently elevated ALT, HCV RNA positivity (Roche Amplicore) and liver histology were tested for: anti-smooth muscle antibodies (SMA), anti liver/kidney microsomal antibodies (LKM), antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-thyroid microsomal antibodies and rheumatoid factor (RF). All pts were caucasian and born in the UK. **Results:** all pts were AMA and LKM negative

	ANA	SMA	thyroid
male	0/59	2/59*	1/59
female	1/42*	2/42*	2/42
tot/%	1/101 (1%)	4/101 (4%)	3/101 (3%)
	RF<40	40<RF<640	RF>640
male	14/59	6/59	1/59
female	8/42	4/42	7/42 #
tot/%	22/101 (21.4%)	10/101 (10.2%)	8/101 (7.1%)

*titre<40, #p<0.01 (female vs male)

In SMA+ve and ANA+ve pts the overall biochemical profile did not show features of autoimmune chronic hepatitis. 2/4 SMA+ve and the ANA+ve pt had liver biopsies which confirmed HCV etiology. **Conclusions:** 1) The prevalence of antitissue antibodies among our pts is very much lower than overseas case series. 2) Although the prevalence of RF was lower than elsewhere it was detectable in 37.7% of pts in keeping with the hypothesis that HCV can cause a benign proliferation of B cells.

W62

INTERFERON (IFN) SPARING EFFECT OF ADJUVANT TAUROURSODEOXYCHOLIC ACID (T-UDCA) FOR TREATMENT OF CHRONIC HEPATITIS C. RESULTS ON LIVER HISTOLOGY.

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Long-term IFN administration combined with a dose tapering strategy has been reported to be the most effective treatment for chronic hepatitis C (Hepatology 1995; 22: 700-6). Based on a dose tapering strategy, we have previously reported an IFN sparing effect of adjuvant t-UDCA administration (Hepatology 1996; 24: 403A) as judged on serum transaminases, but the effect on liver histology was not assessed.

The aim of the present study was to assess the effect on liver histology of a strategy combining t-UDCA adjuvant therapy with 6 months full dose IFN followed by further 6 months IFN dose tapering.

121 patients with chronic hepatitis C have been randomised to receive either lymphoblastoid IFN alone (3 MU/m²/i.w. (regimen A) or IFN + t-UDCA (10 mg/kg/day) (regimen B) for 6 months, followed by further 6 months IFN dose tapering for responders (ALT < 1.5 upper limit of normal). Control liver biopsies were carried out 6 months after stopping IFN, while t-UDCA was maintained for regimen B. Disease grading and staging was assessed by the Ishak score system (J Hepatol 1995; 22: 696-9).

68 patients have been presently followed up for 18 months, and the proportion of responders was similar for regimens A and B (19/32 and 21/36 respectively, NS). 43 patients have had repeat biopsy at 18 months. Histological grading decreased from 7.5 ± 0.8 pre-treatment to 5 ± 0.9 during regimen A (n = 22, p<0.03) and from 7.3 ± 0.8 to 4.9 ± 0.8 during regimen B (n = 21, p<0.03). Staging remained unchanged before and during treatment at 2.2 ± 0.4 vs 2.0 ± 0.4 respectively for both regimens. As a result of dose tapering, 6 month cumulative IFN dose was higher in patients treated with IFN alone (583 ± 21 MU) than in those treated with IFN + t-UDCA (505 ± 8 MU, p<0.002).

Our results indicate that adjuvant t-UDCA has an IFN sparing effect, with improvement of liver histology similar to that achieved with higher IFN doses. We conclude that it may be worth further testing the IFN sparing effect of t-UDCA by extending the dose tapering strategy to the whole treatment period.

W64

PLASMA TIMP-1 LEVELS INCREASE WITH SEVERITY OF LIVER DISEASE IN CHRONIC HEPATITIS C.

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BACKGROUND A non-invasive and easily repeatable test of liver disease activity in chronic hepatitis C would be valuable, especially in patients with bleeding disorders in whom liver biopsy has increased risks. As chronic liver disease progresses, there is an imbalance between synthesis and breakdown of extracellular matrix (ECM). Tissue inhibitor of metalloproteinase-1 (TIMP-1) is one of a group of enzymes which inhibits metalloproteinases and are involved in the breakdown of ECM. We have measured TIMP-1 activity in patients with chronic hepatitis C and compared this with liver histology.

METHODS: Plasma TIMP-1 levels were measured using a specific sandwich enzyme immunoassay kit (Amersham UK) in 10 patients with mild chronic hepatitis, 9 patients with severe chronic hepatitis or cirrhosis and 14 controls with normal liver function tests. Liver biopsies on the patients with hepatitis C were scored for a histological activity index by an independent observer, blind to clinical details or TIMP-1 results.

RESULTS: Plasma TIMP-1 levels in patients with severe liver disease (848.5 ng/ml ± 351.2) and with mild liver disease (533.1 ng/ml ± 313.6), were elevated compared to controls (187.1 ng/ml ± 62.2), p<0.05. TIMP-1 levels in patients with severe liver disease were significantly higher than in those with mild liver disease, p<0.05. (mean ± S.D.)

CONCLUSION: Plasma TIMP-1 levels increase with severity of liver disease in chronic hepatitis C. The data suggest that plasma TIMP-1 measurements maybe used as a non-invasive indicator of disease activity in chronic hepatitis C.

W65

OUTCOME OF ORTHOTOPIC LIVER TRANSPLANTATION IN HAEMOPHILIA

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Introduction Many haemophiliacs have developed cirrhosis or hepatocellular carcinoma (HCC) due to chronic hepatitis B and/or C virus infection (HBV/HCV) transmitted from clotting factor concentrates; the outcome of those who have required orthotopic liver transplantation (OLT), is assessed.

Methods Transplant centres of patients identified by medical database search were contacted and survival data assessed by Kaplan-Meier analysis.

Results Twenty-five male haemophiliacs, mean age 39 years (range 5-63 years) underwent OLT in 15 centres between 1982 and 1996. Indications for transplantation were HCV cirrhosis (68%), HBV cirrhosis (16%), HCC (12%) and biliary atresia (4%). Six patients (24%) were HIV positive pre-OLT; one had suffered an AIDS-defining illness. Post-OLT, the mean time to normal clotting factor levels was 18 hours (range 0-48 hours) and exogenous clotting factors were stopped at a mean of 49 hours (range 0-480 hours). Four patients had bleeding complications despite normal clotting values. The 1 and 3 year survival of 6 HIV positive recipients (67% and 23%) was significantly less ($p=0.0003$ each time-point) than that of 19 HIV negative recipients (90% and 83%); 2 of the 5 HIV positive deaths were due to HIV-unrelated causes. Coagulopathy was cured in all 23 patients who survived more than 10 days post-OLT. Six of 16 patients (37%) with HCV cirrhosis pre-OLT developed biopsy-proven HCV at a mean of 9 months post-OLT. Three of the 4 HBV positive patients also developed disease recurrence.

Conclusions OLT cures the coagulopathy of haemophilia. HCV cirrhosis is the commonest indication for OLT but outcome may be complicated by the effects of HIV co-infection or by graft-recurrence of HCV.

W67

ABERRANT EXPRESSION OF P53 AND KI-67 DURING ACUTE AND CHRONIC REJECTION FOLLOWING ORTHOTOPIC LIVER TRANSPLANTATION

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Apoptosis and proliferation are important in regulating immune responses such as allograft rejection. Unlike apoptosis, proliferation and its role have not been investigated in hepatic graft rejection thus far. Ki-67 is a common marker of cell growth, while p53 is able to inhibit cell growth and induce apoptosis as a response to DNA damage. **Aim:** To study the expression of p53 and Ki-67 in the liver tissue during acute and chronic rejection (AR/CR). **Methods:** Paraffin-embedded liver biopsies of 10 patients with AR before/after treatment with i.v. steroids and of 13 patients with CR were studied by immunocytochemistry, using mononuclear antibodies against p53 and Ki-67. Results were assessed semi-quantitatively and compared to normal controls. **Results:** p53 was expressed in hepatocytes, bile ducts (BD) and cells of the inflammatory infiltrate during AR and CR, while no reactivity was detectable in normal controls. Treatment with steroids did not affect the expression. Staining for Ki-67 showed an increased expression in inflammatory cells and hepatocytes during both types of rejection compared to controls, while bile ducts reacted sporadically only during chronic rejection. Steroid treatment reduced the number of Ki-67 positive cells of the inflammatory infiltrate. **Conclusion:** The expression of Ki-67 indicates, that during acute and chronic rejection proliferation is upregulated in both, infiltrating inflammatory cells and parenchymal cells. Additional immunosuppressive therapy suppresses the proliferation of the inflammatory cells. p53 seems to be implicated in the immune response, either as a response to the increased proliferation rate or to accumulation of genome damage.

W66

SERUM GLUTATHIONE-S-TRANSFERASE α (GST) IN ACUTE LIVER ALLOGRAFT REJECTION

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Introduction/Aim: GST has been suggested as a sensitive marker of cellular rejection. This study was performed to determine the utility of GST as a marker of acute rejection.

Methods: Daily measurements of serum transaminases and GST (enzyme immunometric assay, Biotrin) were prospectively recorded in 23 consecutive liver transplant recipients for the first 20 days post transplantation. 56 liver biopsies performed following clinical/biochemical deterioration in liver function; 38 showed acute rejection.

Results: GST peaked on the 2nd day (median 125 μ g/l, range 75-321 μ g/l) after transplant and preceded the ALT peak by one day. GST levels then steadily declined, reaching baseline by day 6 and plateauing till day 8. Even after the initial peak, GST correlated well with the ALT in the majority of patients median correlation coefficient of 0.6 (IQ range 0.45-0.77); and with the bilirubin, median correlation coefficient 0.47 (IQ range 0.14 to 0.6). There was no significant difference in the GST levels between rejection and other causes of hepatic dysfunction on each of 3 days preceding, and the biopsy day. ALT levels had a high sensitivity for rejection (97.4%) but a low specificity (16.7%) GST did not improve these values. In 16 patients treated for moderate/severe rejection, the improvement in the histological score of rejection was not associated with a consistent change in GST.

Conclusion: GST does not offer any advantage compared to ALT in diagnosing rejection or determining response to treatment of rejection.

W68

GRAFT DYSFUNCTION ASSOCIATED WITH AUTOIMMUNITY IN PAEDIATRIC LIVER TRANSPLANTATION

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Over a five-year period of observation seven children (3% of 220 liver transplant recipients) developed an unexplained but characteristic form of graft dysfunction. Five were male and the median age at presentation was 10.3 years (range 2-19.4). The median period after surgery was 24 months (range 6-45). The indication for transplantation were extrahepatic biliary atresia (4), Alagille's syndrome (1), drug induced fulminant liver failure (1) and alpha-1-antitrypsin deficiency (1). Four were on triple immunosuppression with cyclosporin A, azathioprine and prednisolone, while three were on tacrolimus. Infectious and surgical complications were excluded. Liver biopsy showed the histological changes of chronic active hepatitis including portal and periportal hepatitis with lymphocytes and plasma cells, bridging collapse, perivascular cell necrosis without changes typical of acute or chronic rejection. All patients had increased levels of immunoglobulin G [median 23.7 g/L (range 17.2-34.4)] and elevated titres of autoantibodies. All but one responded to prednisolone 2 mg/kg/day and increase or addition of azathioprine (1.5-2 mg/kg/day) within a median period of 22.5 days and remained in remission on a reduced dose of prednisolone (0.05-0.1 mg/kg/day) and the same dose of azathioprine during follow up (median 250 days).

Our data show that manifestations diagnostic of autoimmune hepatitis, and responsive to the classical treatment for this condition, can appear in liver transplant patients while on immunosuppression. Whether autoimmune manifestations precede, and may be the cause of, graft dysfunction remains to be established in a prospective study.

W69

AUXILIARY LIVER TRANSPLANTATION FOR METABOLIC DISEASES

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Liver transplantation has been used successfully to replace the defective or missing enzyme/protein or receptor site in liver-based metabolic disorders. The majority of these disorders produce cirrhosis and total liver replacement is required. There are, however, some non-cirrhotic disorders, such as Crigler-Najjar Syndrome Type 1 (CNS1) where although liver replacement has been successful, auxiliary liver transplantation (ALT) offers the prospect of correcting the metabolic defect, whilst retaining sufficient native liver to support life if the graft fails and also retains the potential for gene therapy in the future.

5 children with CNS1 and 1 child with propionic acidemia (PA) underwent ALT, median age 8 years (range 1-13); median weight 25kg (range 10-49). Median serum bilirubin at ALT for CNS1 was 270 $\mu\text{mol/l}$ (range 222-418) despite 16 hours of phototherapy daily. The child with PA had recurrent hyperammonemic coma on a protein-restricted diet with ammonia levels of 80 $\mu\text{mol/l}$.

Orthotopic left lateral segment ALT was performed in 4 cases and right orthotopic ALT in 1 patient with CNS1 and in the child with PA. Patients with CNS1 had median serum bilirubin levels on day 5 post-transplant of 50 $\mu\text{mol/l}$ (range 32-92) and 30 $\mu\text{mol/l}$ (range 20-45) at a median follow-up of 16 months (range 6-39). The child with PA is on a normal diet with normal serum ammonia levels at 6 months.

Complications included severe acute rejection in 3 patients requiring conversion to FK506 and the late development lymphoproliferative disease (LPD) in one due to EBV infection. He was retransplanted successfully after the first ALT but died 4 months later from extensive LPD. We have shown that it is possible to correct the metabolic errors abnormalities in CNS1 and PA with ALT. Other non-cirrhotic inborn errors of metabolism are also suitable for ALT, but the volume of liver tissue required for a successful outcome may depend on the disease.

W71

LONG-TERM SURVIVAL AND ALCOHOL RELAPSE AFTER LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE. S.P. Pereira¹, P. Muiresan², L. Howard³, M. Rela², N. Heaton², Roger Williams¹. ¹Institute of Liver Studies, ²Liver Transplant Surgical Service and ³Department of Psychological Medicine, King's College Hospital, London SE5 9RS.

Short-term survival rates after orthotopic liver transplantation (OLT) for end-stage alcoholic liver disease (ALD) are reported to be similar to those for other chronic liver diseases. However, the frequency of alcohol relapse, and its effects on long-term graft and patient survival, remain unclear.

Aims: To review the outcome of transplantation for ALD in a single centre over the past 10 years, with particular emphasis on survival and recidivism after OLT. **Methods:** From Jan 1987 to Sept 1996, 111 patients (98M, 13F; mean age 51 yr, range 33-69 yr) underwent OLT for Child's B or C alcoholic cirrhosis, after an alcohol abstinence of > 6 months. In 89 patients (80%), alcohol was the only aetiological factor, while 20 (18%) also had chronic B or C hepatitis and 17 (15%) had developed hepatoma as a complication of ALD. Post-transplant, alcohol relapse was assessed by outpatient and case note review, and by a Severity of Alcohol Dependence Questionnaire sent to transplant survivors. **Results:** 19 deaths (all males) occurred in the first 3 months -- due to sepsis or cardiac complications in 14 (74%). A further 12 patients (10M, 2F) died 0.9-7.5 yr (median 1.6 yr) post-transplant, most frequently due to hepatoma recurrence (n=3) or other malignancies (n=4). The actuarial survival rate for the 111 patients was 79% at one year, and 64% at 5 years -- compared with figures of 76% and 69% in 700 patients transplanted for other chronic liver diseases. Of the 92 patients who survived at least 3 months post-transplant, 18 (20%) reported at least one episode of drinking > 3 units daily, while a similar number admitted to 'social' drinking, after a median period of abstinence of 9 months. Five patients developed recurrent alcoholic cirrhosis/graft failure within 5 years -- two of whom died at 10-24 months. **Conclusions:** Long-term survival after OLT for ALD is similar to that for other liver transplant recipients. In our experience, alcohol relapse occurs in a large minority of patients, though at lower levels of alcohol intake than previously. In those with problematic drinking post-transplant, graft damage occurs rapidly.

W70

CLINICAL OUTCOME AND FLOW CYTOMETRIC (FACS) IGG CROSSMATCH IN LIVER TRANSPLANTATION.

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Introduction: The role of preformed donor-specific IgG allo-antibodies in kidney and heart grafts is well established. However, although a number of recent studies have suggested that these antibodies may increase the risk of both rejection and early graft failure in liver transplants,^{1,2} this remains controversial.³ The differences between studies may simply reflect variations in the sensitivity of methods used to detect these antibodies. In the present study we have sought correlation between preformed IgG antibodies and clinical outcome using two different crossmatch techniques. **Methods:** Between May 1995 and June 1996, 82 adult liver allograft recipients (34 females, 48 males) were examined for the presence of pre-formed donor-specific IgG allo-antibodies using flow cytometry (82 cases) and a standard microcytotoxicity assay (65 cases). **Results:** A flow cytometric crossmatch was detected in 18/82 (22%), however only 9/15 flow cytometric antibody positive patients were antibody positive by cytotoxicity assay. Patients with FACS positive crossmatches were more likely to develop two or more episodes of acute cellular rejection (4/18 cf 4/64, $p = 0.044$, RR = 4.29), and more likely to develop hepatic artery thrombosis (3/18 cf 1/64, $p = 0.009$, RR = 12.6). At follow-up survival was 80% in those who were FACS negative and 67% in those with FACS positive IgG antibodies. However, despite a clear trend the survival analysis did not reach statistical significance ($p = 0.31$). **Conclusions:** These results confirm the greater degree of sensitivity of flow cytometry for the detection of IgG positive crossmatches and suggest that flow cytometry may help predict those at risk of developing severe graft rejection or hepatic artery thrombosis.

¹Takaya et al. Transplantation 1992; 53: 400.

²van Hoek et al. Semin Liver Disease 1992; 12: 41.

³Donaldson et al. Transplantation 1995; 60: 1016.

W72

EFFECT OF ABRUPT ALCOHOL WITHDRAWAL ON LIVER TRANSAMINASES AND MARKERS OF LIVER FIBROSIS

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Introduction: It has been suggested that liver function tests (LFT's) may worsen in alcoholics following abrupt withdrawal from alcohol but evidence for this is limited. We assessed LFT's and two markers of hepatic fibrosis; pro-collagen III peptide (PIIP) and tissue inhibitor of metalloproteinase 1 (TIMP1) in patients admitted to an alcohol rehabilitation unit.

Method: We recruited 24 patients with a history of alcohol abuse, but no evidence of liver disease of another cause. Seven consecutive daily blood samples were obtained. Measurements of nutritional status and withdrawal severity were made. Our arbitrary criteria for worsening of LFT's were: a 50% rise from baseline value with the elevated value above the laboratory normal reference range

Results: 7 out of the 24 subjects (29.2%) showed worsening of their LFT's (95% confidence interval 11.0%-47.4%). These patients all showed a rise in both AST and ALT of similar proportion, but not of gamma GT, bilirubin, alkaline phosphatase, creatine kinase or CRP. There was no significant difference between the group who showed worsening and the others who tended to show improving transaminases with respect to baseline clinical, nutritional or laboratory findings, or short-term outcome.

PIIP levels increased in both groups from day 1 to day 7 ($P=0.05$). TIMP1 levels tended to rise in the group with worsening transaminases, but tended to fall in the other group. ($P=0.09$)

Conclusion: This study confirms the clinical impression that worsening of AST and ALT is common in alcohol withdrawal. Alcohol withdrawal is associated with a rise in PIIP, and a rise in TIMP1 in those with worsening transaminases. We conclude that acute alcohol withdrawal may be associated with an increase in hepatic fibrosis.

Nutrition W73-W82

W73

WHY DO PATIENTS WITH WEIGHT LOSS HAVE A WORSE OUTCOME WHEN UNDERGOING CHEMOTHERAPY FOR GASTROINTESTINAL MALIGNANCIES?

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(HUNA is funded by the BDF) the Gastrointestinal Unit, Royal Marsden Hospital & the CRC Centre of Cancer Therapeutics, Institute of Cancer Research, Sutton, Surrey.

Aims: To examine whether weight loss at presentation for chemotherapy for gastrointestinal carcinomas influences outcome and whether nutritional intervention could be worthwhile.

Methods: Data were gathered prospectively. The outcomes were compared of patients with or without weight loss treated for locally advanced or metastatic tumours of the oesophagus, stomach, pancreas, colon or rectum.

Results: Of 1,555 consecutive patients included, weight loss was reported more commonly by men (51%) than women (44%) at presentation (p=0.01). Patients with weight loss received less chemotherapy but developed more frequent and more severe dose limiting toxicity - plantar-palmar syndrome (p<0.0001) and stomatitis (p<0.001) - than patients without weight loss. Consequently, patients with weight loss on average received 1 month less treatment (p<0.0001). Weight loss correlated with shorter failure free (p<0.0001, Hazard Ratio=1.25) and overall survival (p<0.0001, Hazard Ratio=1.63), decreased response (p=0.006), quality of life (p<0.0001) and performance status (p<0.0001). Patients who stopped losing weight had better overall survival (p=0.0004). Weight loss at presentation was an independent prognostic variable (Hazard Ratio =1.43).

Conclusions: The poorer outcome from treatment in patients with weight loss appears to occur because they develop more toxicity, have more breaks from treatment and receive significantly less chemotherapy rather than any specifically reduced tumour responsiveness to treatment. Randomised nutritional support intervention studies are urgently required in these groups of patients.

W75

Randomised Double-blind trial of polymeric versus elemental diet in treatment of active Crohn's disease.

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Enteral nutrition is now accepted as a primary therapy for active Crohn's disease. Open comparisons have suggested that polymeric diets (PD) are as effective as elemental preparations (ED). This double-blind controlled trial is designed to compare the therapeutic efficacy of a multi-protein polymeric diet with an amino-acid based elemental diet in treatment of active Crohn's disease.

Patients with established active Crohn's disease (CDAI > 150, raised CRP, increased bowel uptake of Tc-99m HMPAO labelled WCC) were randomised to received either a polymeric diet or a matched elemental diet (Scientific Hospital Supplies, Liverpool, UK). The two diets were identical except for protein contents (intact proteins in PD and free aminoacids in the ED). Enteral nutrition was delivered via a fine bore nasogastric tube for a period of 4 weeks with a mean daily caloric intake of 2500 kcal. Only tap water was allowed during enteral feeding. Remission is defined as a final CDAI < 150 or a reduction in CDAI by at least 100 points from base line, normal CRP levels and avoidance of steroids or surgery.

Sixteen patients were enrolled into this study. Eight patients received the polymeric diet and another eight an elemental preparation. There was no significant difference between the two treatment groups at entry in respect of age, disease location, initial CDAI and CRP levels, body weight, nutritional status and extent of bowel uptake on the labelled WCC scans. Six and seven patients achieved remission with polymeric and elemental diets respectively. The changes in CDAI and inflammatory markers are shown below:

	ED		PD	
	0	4	0	4
CDAI	362±77	130±31	328±30	96±15
CRP	18±4	5±1	78±27	5±1
Hb	12.2±.38	12.8±.4	11.1±.9	12.5±.4
Albumin	40±1.3	42.7±.9	41.8±1.9	45.5±.35
ESR	36±10	20±7	53±16	40±11

* (mean ± SEM)

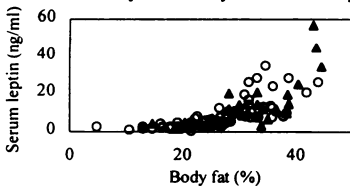
The fall in bowel activity on Tc-99m HMPAO imates was not different in the two groups. The over all remission rate achieved with enteral nutrition was 85%.

Enteral nutrition is well tolerated and effective in control of active Crohn's disease. Differences in protein content of enteral feeds are not relevant to their therapeutic efficiency as polymeric and elemental diets are equally effective.

W74

SERUM LEPTIN IN INFLAMMATORY BOWEL DISEASE (IBD): IMPLICATIONS FOR THE PATHOGENESIS OF ANOREXIA AND WEIGHT LOSS. AB Ballinger, E.M. Hallyburton, R.Besser, EM Alstead, MJG Farthing, Digestive Diseases Research Centre, St Bartholomew's & The Royal London School of Medicine & Dentistry, London UK.

INTRODUCTION: IBD is frequently associated with loss of appetite and body weight. Healthy individuals, however, adjust their appetite and maintain their body weight within a narrow range. It is proposed that this control is due in part to leptin, a newly described hormone, which is secreted by fat cells and acts in the CNS to suppress appetite. In animals, administration of IL-1β and TNF-α, which are both implicated in inflammatory cachexia, increase circulating leptin levels and induce anorexia and weight loss. The aim of this study was to explore the hypothesis that patients with IBD in relapse fail to increase their appetite in response to weight loss due to inappropriately raised serum leptin concentrations. **METHODS:** Serum leptin concentrations were measured by radioimmunoassay in 35 (17 men) control subjects and 72 patients (34 men; 52 Crohn's, 20 UC) with IBD. Body mass index and % body fat was recorded. Loss of appetite was assessed on a 4 point scale from "not at all" (score 0) to "very much" (3). Disease activity was assessed clinically and by measurement of the ESR and C-reactive protein. **RESULTS:** Serum leptin concentrations in the controls was 8.0 (3.1-14.1ng/ml, median [interquartile range]) and 4.8 (2.6-10.1ng/ml) in the IBD patients. Serum leptin concentrations were highly correlated with % body fat (figure) in the control group (r = 0.84, P = 0.03) and IBD patients (r = 0.82, P 0.006); the difference in leptin concentrations between the two groups was accounted for by lower body fat in the IBD patients.



The relationship between % of body fat and serum leptin concentrations in 35 control subjects (▲) and 72 patients with IBD (○). The regression lines (not shown) for the 2 groups of patients were almost superimposed.

12 patients (6 men) had moderate/severe anorexia (grade 2/3) associated with a disease relapse (ESR>30mm/h, CRP>40). Serum leptin of these patients (4.3[3.2-8.1ng/ml]) was no different when compared to healthy and quiescent disease controls (5.3[3.5-10.6ng/ml]) matched for sex and % body fat (mean 24.2%, range 4.8-43.9). **CONCLUSION:** Serum leptin is appropriately suppressed in patients with anorexia and IBD. In contrast to the animal work, this study does not support a role for leptin in cachexia associated with IBD.

W76

RAPID COLONIC FERMENTATION IS ASSOCIATED WITH SYMPTOMS IN IBS AND CORRECTED BY EXCLUSION DIET.

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Introduction: Use of an exclusion diet reduces symptoms in 50% of IBS patients. Food intolerance is unlikely to be immunologically mediated but may be related to colonic fermentation. **Methods:** 5 female IBS patients and 4 female controls followed two fixed diets (12.5g NSP, 128g starch, 3.6g resistant starch/day; 8MJ/d. adjusted to estimated TEE; protein:carbohydrate:fat 15:45:10) : a standard western diet (STD) followed by an exclusion diet (EXN), in which common sources of food intolerance were prohibited. Subjects followed each diet for 14 days, with a 2 week wash-out period. Food diaries were filled daily and all meals were provided from a metabolic kitchen for the last 7 days of each diet. A symptom score was calculated daily. On the last day of each diet total excretion of hydrogen (H₂) and methane (CH₄) were measured for 24 hours in a purpose-built and validated 1.4m³ whole-body calorimeter. Breath H₂ and CH₄ concentrations following 20g lactulose were also measured on each diet. **Results:**

	mean symptom score	mean total H ₂ ml/24hrs	mean total CH ₄ ml/24hrs	mean total rate ml/min	max total rate ml/min
patients std	8.3	361	152	0.4	2.5
exn	5.9	90	84	0.1	0.4
controls std	1.3	147	266	0.3	0.7
exn	1.5	86	480	0.4	1.2

Rapid gas excretion in the calorimeter was associated with onset of symptoms. Breath concentrations of H₂ and CH₄ after lactulose altered in parallel with changes in 24-hour gas excretion in 4/5 patients and 3/4 controls. **Conclusions:** 1) Symptoms are associated with rapid excretion of H₂ and CH₄, and improvement of symptoms by diet coincides with reduced excretion. 2) The effect of diet on methanogenesis is variable. 3) The reduction in H₂ excretion with exclusion diet is consistent with the expected low colonic availability of easily digestible rice starch. However changes in gas excretion during lactulose breath tests demonstrate that qualitative changes in colonic fermentation also occur. These factors may explain the efficacy of exclusion diets in IBS.

W77

A RANDOMISED DOUBLE BLIND PROSPECTIVE STUDY OF LONG CHAIN TRIGLYCERIDE (LCT), MCT/LCT AND MEDIUM CHAIN TRIGLYCERIDE (MCT) DURING PARENTERAL NUTRITION

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The best non-nitrogen calorie source during parenteral nutrition remains controversial. This study was performed to establish whether the use of a 20% MCT emulsion would demonstrate significant advantages over conventional LCT.

Following a volunteer study establishing the safety of a 20% MCT emulsion (B.Braun Melsungen) ethical committee approval was obtained for a prospective study. Fifty seven patients were randomised to receive conventional 20% LCT, 10% MCT/10% LCT or 20% MCT as 50% of their non-nitrogen calories during routine TPN. Patients were studied for 10 days after which all patients reverted to our standard TPN regimen.

Results were analysed by analysis of covariance of the final day measurement with respect to the initial value for each variable, prior to breaking the randomisation code. There were no adverse clinical reactions in any of the groups. Cardiovascular and respiratory parameters and routine haematological, biochemical and acid base measurement were unchanged. Differences were demonstrated in bilirubin levels where LCT (72.3 ± 31 mmol/l mean \pm sem) was significantly higher than MCT (19.6 ± 6.1) or MCT/LCT (23.4 ± 12.5), ($p = 0.025$). Levels of free glycerol were also reduced in the LCT group (1.28 ± 0.1 mmol/l) compared with MCT (2.48 ± 0.23 and MCT/LCT (2.67 ± 0.27) $p < 0.001$). There was also a trend towards a higher white blood cell count in the LCT group.

This study demonstrates that 20% MCT emulsions are safe for routine clinical use and also suggests that MCT or MCT containing emulsions have advantages metabolically and on liver function.

W79

GASTROESOPHAGEAL REFLUX IN PATIENTS FED BY PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG) - SCINTIGRAPHIC DETECTION.

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Percutaneous endoscopic gastrostomy (PEG) is the method of choice for long-term enteral nutrition in patients unable to swallow due to a variety of medical conditions. PEG eliminates the need for surgical gastrostomy and nasogastric tubes, is easily performed with few demands on health service resources. Aspiration pneumonia may complicate PEG insertion but there are few studies on gastroesophageal reflux (GOR) in PEG patients.

Methods: 22 patients (14 M, 8F, age 43-83 yrs, median 69) with PEG underwent radionuclide GOR studies. 13 patients had neurological and 9 had mechanical dysphagia. They received 100 ml of orange juice containing 25 MBq of 99m Tc colloid followed by 300ml of normal saline through the PEG tube. Patients lay supine under the gamma camera linked to a digital computer system. 4 min. and 4 h images over stomach, oesophagus and lungs were examined for GOR and lung aspiration.

Results: 10 patients, 8 of whom with neurological dysphagia and 2 of whom with mechanical dysphagia, had severe GOR. 2 other patients with neurological dysphagia had mild GOR. One patient with severe GOR also had lung aspiration at 4 hrs. 10 patients had normal studies.

Conclusions: 1) Radionuclide imaging is useful in assessing GOR in PEG patients 2) GOR appears to be a major problem in patients with PEG and 3) PEG patients with neurological dysphagia appear to be at greater risk for GOR than those with mechanical dysphagia.

W78

OPTIMISING CATHETER SURVIVAL IN PERIPHERAL PARENTERAL NUTRITION: A RANDOMISED CONTROL TRIAL

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Peripheral vein thrombophlebitis (PVT) is a major obstacle to successful and prolonged administration of peripheral intravenous nutrition (IVN). This study assesses the impact of glyceryl trinitrate (GTN), heparin & hydrocortisone and a combination of both therapies on the incidence and time to onset of PVT during the administration of standard (1200 osm/kg) peripheral IVN via a fine bore polyurethane catheter. One hundred and eleven patients were randomised to receive standard peripheral nutrition with either a 5mg GTN patch directly over the catheter tip (Group 1, n=42), heparin 1500 iu & hydrocortisone 15mg added to the infusate (Group 2, n=40) or a combination of all three interventions (Group 3, n=29). Limbs were examined daily and catheters removed if any signs of PVT became evident (pain, swelling, erythema, tenderness, increase in temperature, or a palpable venous cord). The three groups were matched for age, gender, indications for IVN and total duration of nutritional support.

The use of a GTN patch alone (group 1) was associated with a shorter time to onset and higher incidence of PVT than either of the other groups (median catheter survival 6 days (group 1) vs 10 days (groups 2&3); $p < 0.03^*$). There was no additional benefit of GTN in addition to heparin & hydrocortisone alone ($p = ns^*$ Group 3 vs Group 2). In addition, choice of vein significantly influenced catheter survival, since significantly lower incidence of PVT and longer duration to develop PVT was observed when the basilic vein was used (compared to the cephalic vein) in all 3 study groups (median catheter survival 10 days (basilic vein) vs 6 days (cephalic vein); $p < 0.01^*$).

In conclusion, a GTN patch alone, and the addition of a GTN patch to heparin & hydrocortisone in the infusate, offer no benefit in terms of peripheral catheter survival. We would recommend peripheral feeding using heparin & hydrocortisone in the infusate using the basilic vein whenever possible to optimise catheter survival and reduce morbidity. (*Chi squared and Log Rank statistics)

W80

SMALL BOWEL JUICE DISACCHARIDE ACTIVITY IN THE PRE-TERM INFANT

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Conflict exists regarding the efficiency of lactose hydrolysis in the premature newborn. Lactase activity in the foetus appears low, but preterm infants fed lactose containing formula usually grow without losing carbohydrate in the stool. Experimental data both supporting and refuting efficient lactose hydrolysis is generally derived using indirect assessments. A more direct approach is to measure disaccharidase activity in duodenal fluid or mucosa. One study of 8 infants from 26 - 29 weeks gestation suggested that during the first 3 weeks of life, lactase activity increased and from the outset was comparable with older children. We have obtained duodenal aspirates from preterm infants over the first 2 months of life. 40 infants were studied; median (range) gestational age 29 weeks (24 - 40) and birthweight 1260 g (600 - 2550). 31 were appropriately grown and 9 were small for gestational age. Disaccharidases were measured by a 2 step colourimetric assay using a standard Boehringer Mannheim kit. 34/56 (61%) of lactase, 44/56 (79%) of maltase and 23/56 (42%) of sucrase activities fell below the lower published reference range for older children. There was no apparent increase in enzyme activities or fall in sucrase:lactase ratio with increasing postnatal age. Despite this, none of the children showed clinical evidence of carbohydrate malabsorption. We conclude that disaccharidase activities are frequently low in the preterm enterally fed newborn compared with older children, however, the absence of clinical evidence of lactose malabsorption suggests that undigested lactose is assimilated in the colon. There is probably no reason for preterm formula milks to contain less lactose than breast milk as many do at present.

W81

Intestinal transit and release characteristics of pancreatin enzyme microspheres.

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Mismatch in gut transit between food and pancreatin may be relevant to recent reports of colonic strictures in cystic fibrosis (CF) patients. We investigated the gastric emptying and small bowel transit of food and pancreatin in 10 pancreatic insufficient CF patients aged 9 to 38 years (of whom four in group 1 had good and six in group 2 had suboptimal nutritional status). Twin-channel scintigraphy combined with breath hydrogen sampling was used to track the concurrent movement of indium labelled pancreatin microspheres and an standard technetium labelled semi solid test meal. Small bowel transit time for food was established by incorporating a hydrogen source within the test meal.

Patient group	Median Wt SD score	Median small gut transit time	Median 50% emptying FOOD	gastric time: ENZYME
1 (n=4)	+0.4	2.8hr	88min	99min
2 (n=6)	-2.6	4.0hr	133min	36min

Small bowel transit for food was delayed (>6 hours) in 3 subjects. The difference in gastric 1/2 emptying time between enzymes and food was significantly greater (range 47-195 min) in patients with suboptimal nutritional status ($p=0.03$, $df=1$, Fishers exact probability test). Enzyme "hot spots" in 2 subjects were visualised in the colon by 2 hours. This discrepancy in transit of pancreatic enzyme microspheres and food boluses could account for continuing malabsorption in some CF patients and identify a mechanism whereby intact microspheres reach the colon.

Inflammatory bowel disease W83-W104

W83

HIGH PREVALENCE OF UNDETECTED INFLAMMATORY BOWEL DISEASE (IBD); DATA FROM THE NOTTINGHAM FAECAL OCCULT BLOOD (FOB) SCREENING TRIAL

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The severity of symptoms from IBD can vary from devastating to none and a previous study from the Nottingham FOB screening trial suggested that the prevalence of asymptomatic IBD might be substantial (GUT 1989;30:481-483). The screening trial has now been completed. The aim of this study is to reassess the prevalence of IBD detected in the trial.

FOB tests were performed by 44,838 of the 75,253 subjects aged 49-74 offered screening. Patients known to have IBD were excluded from FOB screening. All subjects FOB positive on one or more occasions ($n=1778$) were investigated by colonoscopy or flexible sigmoidoscopy and barium enema. 94 were found to have IBD at endoscopy and confirmed by histology. 57 subjects had previously undetected IBD (55 ulcerative colitis (UC), 2 Crohn's disease (CD)). The remaining 37 (31 UC, 6 CD) had had a previous diagnosis of IBD but this had not been recognised when they were invited to be screened. The prevalence of previously undetected IBD in those offered screening was $73/10^5$ (95%ci 54-92/ 10^5) for UC and $2.7/10^5$ (95%ci 0.3-10/ 10^5) for CD. Based on those accepting screening the prevalence of undetected UC was $123/10^5$ (95%ci 90-155/ 10^5) and for CD $4.5/10^5$ (95%ci 0.5-16/ 10^5). The prevalence of undetected UC was higher in the over 60s and also was almost two-fold higher in men than women (164 v. $87/10^5$). Proctosigmoid UC accounted for 54% (31/57) of cases and pan colitis for 20% (11/57). 82% (47/57) had some symptoms but had not consulted or had not been referred for investigation; 62% reported rectal bleeding and 60% had mild diarrhoea.

The prevalence of undetected UC is much greater than previously reported. Prevalence is higher in men, increases with age, and low-grade symptoms are common. Increased detection of prevalent UC needs to be allowed for in studies of comparing UC incidence.

W82

B VITAMIN DEFICIENCIES MAY BE COMMON IN THE ACUTE INPATIENT POPULATION.

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110 patients were selected at random from those admitted via the Accident and Emergency department over 3 days. Erythrocyte transketolase (ETK), glutathione reductase (EGR) and aspartate aminotransferase (EAA) enzyme assays were used to determine thiamin, riboflavin and pyridoxine deficiencies respectively. A deficiency state was diagnosed when the percentage activation with added coenzyme was greater than the conventionally accepted limits of 23%, 20% or 86% for ETK, EGR, and EAA assays respectively.

77% of patients were under the care of the directorate of General Medicine, 15% General Surgery and 8% Orthopaedics. 56% of the study group were men, 73% Caucasian, 20% Asian and 7% Afro-Caribbean. A total of 66 patients (60%) had at least one biochemical B vitamin deficiency. Of the 17 patients who had a body mass index (BMI) below the desired range of 20-25 kg/m², 15 had one or more deficiencies. The majority of deficient patients, however, had BMI values within the desired range. The median age of the deficient patient group was lower at 59y compared with 69y in the non-deficient group ($p=0.002$, Mann Whitney U test). Overall the prevalences of specific deficiencies were 9%, 41%, 35% and 22% for thiamin, riboflavin, pyridoxine and multiple deficiency states respectively. Four patients were admitted with alcohol related disease; of these two were thiamin deficient and one had combined riboflavin and pyridoxine deficiencies.

B vitamin deficiencies seem common in the acute inpatient population and are not limited to those patients with protein-energy undernutrition.

W84

MORTALITY IN INFLAMMATORY BOWEL DISEASE: THE CASE FOR A NATIONAL CONFIDENTIAL ENQUIRY.
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Introduction Mortality due to inflammatory bowel disease (IBD) has decreased steadily since 1950, but population-based cohort studies suggest that IBD patients continue to have a higher mortality rate than expected, partly due to a higher incidence of gastro-intestinal malignancies. Records held by the Office for National Statistics since 1993 permit detailed analysis of mortality in IBD patients, including calculation of the number continuing to die from complications of the disease itself or from colorectal malignancies.

Methods Patients who died in England and Wales between January 1st 1993 and 31st December 1995 inclusive and whose death certificates included the codes 555 (Crohn's disease/CD) or 556 (ulcerative colitis/UC) were identified from Office for National Statistics records.

Results IBD was listed as a cause of death in 2581 patients, of which 1146 (44%) had CD and (1435) 56% had UC. CD was the underlying cause of death in 462 (40.3%) of patients with CD on their certificate, whereas the figure for UC was 509 (35.0%). The mean age at death for those with CD was 68.2 and 72.3 years (male and female respectively) and 70.7 and 76.0 years (male and female) for those with UC. Of those patients who had CD or UC as their underlying cause of death, 54 (12%) and 25 (5%) were less than 50 years-old, respectively. Colorectal carcinoma accounted for the deaths of 9 (8%) and 23 (24%) of CD and UC patients under 50 years-old, respectively.

Conclusions At least 300 IBD patients per annum in England and Wales continue to die from their disease and its complications despite improved treatment and endoscopic follow-up. Most deaths occur in elderly patients, but a surprisingly high number of younger patients continue to die either from their disease (CD patients) or from colorectal carcinoma (UC patients). Further study, such as by national confidential enquiry, may identify reasons for these deaths and lead to improved survival of IBD patients.

W85

INFLAMMATORY BOWEL DISEASE IN A NATIONAL BIRTH COHORT

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Aims: A birth cohort with prospectively collected data was used to investigate the prevalence of inflammatory bowel disease (IBD) at age 26 years and the association of childhood diseases with subsequent diagnosis of IBD.

Methods: The 1970 British Cohort Study (BCS70) is a longitudinal study of everybody born in Great Britain between 5 - 11 April 1970. A survey of Crohn's disease and ulcerative colitis was conducted at the age of 25/26 years, with 9,800 (85%) responding. Diagnosis of IBD, using standardised criteria, was confirmed by cohort members' physicians and by histology. Reports of otitis media and eczema were collected prospectively at the ages of 5 and 10 years.

Results: By age 26 years, 24 cases of Crohn's disease and 20 cases of ulcerative colitis had been diagnosed, representing prevalence rates of 2.45 and 2.04 per 1,000 respectively. The earliest diagnosis of IBD had been made at age 12 years. Otitis media at 5 years was significantly associated with ulcerative colitis (relative risk=4.00, 1.20 - 13.30), but not Crohn's disease (0.44, 0.06 - 3.31). Eczema at 10 years was associated with ulcerative colitis (4.88, 1.85 - 12.86), but not Crohn's disease (0.81, 0.19 - 3.53).

Conclusions: A very high prevalence of IBD, particularly Crohn's disease, was found amongst British 26-year olds. Otitis media and eczema were significantly associated with future ulcerative colitis, but not Crohn's disease.

W87

TREATMENT OF REFRACTORY INFLAMMATORY BOWEL DISEASE WITH GRANULOCYTE APHERESIS

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Uncontrolled studies have suggested that leucocyte apheresis may be a useful in the treatment of inflammatory bowel disease (IBD). We report the results of a pilot study evaluating the use of granulocyte apheresis in patients who had failed to respond to standard medical therapy.

Eighteen patients with active ulcerative colitis (UC) and six with active Crohn's disease (CD) were recruited. These patients had not responded to prednisolone and, in most cases, azathioprine and 5-ASA compounds. Granulocyte apheresis was performed weekly using a column (G1, Otsuka Pharmaceutical Co. Ltd). Response was assessed by symptom indices, sigmoidoscopy, histological scoring and leucocyte scintiscanning.

In UC, 3 patients went into remission and the overall clinical symptom score for all patients, fell from a median of 9 on entry to 3.5 after four weeks (Wilcoxon P-value=0.012). There was a statistically significant improvement in the mucosal appearance at sigmoidoscopy at entry compared to after four weeks treatment (mean change -0.53, Wilcoxon P-value=0.016). The histological score also improved from a median of 5 to 4 (Wilcoxon P-value=0.096).

One patient with CD withdrew due to dizziness, 1 achieved remission and there was a reduction in the median CDAI score from 306 to 177.5 after four weeks treatment (Wilcoxon P-value=0.09). The leucocyte scintigraphy score also improved from a mean value of 2.5 at entry to 1.5 after four weeks (Wilcoxon test, P-value=0.25). There were no significant change in median haemoglobin, white cell or platelet counts during the study. There were no changes in laboratory values that caused concern and the procedure was well tolerated both by in- and out-patients.

This is the first study looking at granulocyte apheresis in patients with steroid resistant IBD. Our data suggests that the treatment is both feasible and safe and may have been effective in both UC and CD. However, larger, controlled studies are required.

W86

SOCIAL IMPLICATIONS OF CHILDHOOD CROHN'S DISEASE;

GA Moody, JA Eaden & JF Mayberry.

A validated questionnaire investigating quality of life was mailed to the parents of all child members of Crohn's in Childhood (CICRA) (age 5-17). 64 questionnaires were returned along with 35 from patients in the adult age range (not analysed). The mean age of patients interviewed was 14.1 ± 2.8 , (range 6-17), with equal numbers of males to females. The mean duration of illness was 4.9 ± 3.3 years; patients had 1.4 ± 0.7 operations (range 0 - 6). Of the children investigated over half had significant absences from school (60%), with a mean of 3 ± 2.8 months off school in the previous year. Many felt their teachers knew nothing about CD (53%) and that they were unsympathetic (50%). Of the 24 who had taken examinations 80% thought they had underachieved because of ill health.

Patients were asked whether they were able to perform several everyday childhood activities. The following table summarises their responses;

	Sometimes	Never	Always
Play outside with their friends	28 (42%)	5 (8%)	33 (50%)
Go out	37 (56%)	3 (4%)	26 (40%)
Take part in sport	41 (63%)	3 (4%)	22 (23%)
Go on holiday	25 (38%)	0	41 (62%)
Stay overnight at a friends house	25 (38%)	8 (13%)	33 (49%)

The commonest questions asked by the children were (i) what is CD? (50%), (ii) why me? (64%), (iii) will it affect my schooling (52%) and (iv) will it affect my chances of getting a job (67%)

In conclusion children with CD have a significantly impaired quality of life, they fear every day childhood activities and their future. They need sympathetic management and effort should be concentrated on improving their day to day existence to enable them to lead a normal a life as possible.

W88

DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL TO DETERMINE THE EFFICACY OF ESSENTIAL FATTY ACID SUPPLEMENTATION IN THE TREATMENT OF ULcerative COLITIS

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In ulcerative colitis (UC) the colonic mucosa contains pro-inflammatory prostaglandins and leukotrienes. HGA (eicosanoic acid 0.3g; gammalinolenic acid 1.6g; docosahexaenoic acid 0.45g daily) was administered to patients with UC for 12 months in an attempt to increase the synthesis of less inflammatory eicosanoids. Disease activity was assessed at 3-monthly intervals using standard clinical, sigmoidoscopic and histological features. In addition, assessments of secondary parameters; quality of life, weight, diet, adverse events, haematological and biochemical parameters were made. 80 patients were randomised to HGA or placebo on an intention to treat basis and stratified for extent of disease. 58 patients with quiescent UC were randomised to receive HGA (n=29, mean age 41 ± 9 yrs), or placebo (n=29, mean age 43 ± 12 yrs). 20 patients with poorly controlled UC were randomised to HGA (n=9, mean age 44 ± 11 yrs) or placebo (n=11, mean age 43 ± 8 yrs). Secondary parameters such as sex, smoking, allergies and treatment were matched. HGA treatment did not benefit either group of patients (Table).

Months	Active UC % of patients in relapse (95% confidence intervals)		Quiescent UC % patients in remission (95% confidence intervals)	
	Placebo (n=11)	HGA (n=9)	Placebo (n=29)	HGA (n=29)
3	91 (74) (100)	71 (36) (100)	90 (79) (100)	75 (58) (91)
6	91 (74) (100)	71 (36) (100)	86 (60) (91)	48 (36) (74)
12	68 (36) (98)	71 (36) (100)	76 (60) (91)	55 (36) (74)

The time (days) for 25% (lower quartile) of patients with active colitis to enter remission was 275 in placebo and 92 in HGA groups (NS), and that for 25% of patients in remission to relapse was 365 in placebo and 83 in HGA group (NS). There were no differences in secondary parameters. HGA treatment had no clinical benefit in either active or quiescent UC.

W89

A RANDOMISED CONTROLLED TRIAL OF ESSENTIAL FATTY ACIDS (EFA) IN ACUTE ULCERATIVE COLITIS(UC).

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Background: Omega-3 EFA (fish oil) has recently been shown to be beneficial in decreasing relapse rates in Crohn's disease (Beluzzi NEJM 1996; 334:1557). Omega-3 EFA appear to be of more limited benefit in acute ulcerative colitis and possible synergy with omega-6 (plant oil) EFA has been suggested. We therefore carried out a randomised double blind controlled trial of omega-3 and omega-6 EFA supplementation in acute UC to determine if they reduced steroid requirement and to investigate if synergism existed between them.

Methods: Patients with acute relapse of colitis were randomised to receive omega-3 EFA (eicosapentaenoic acid 1.5g), omega-6 EFA (gamma linolenic acid 2.1g), both or placebo daily for four months. Prednisolone use was systematically reduced using a standard withdrawal protocol. As the trial was exploratory, the main analysis was of steroid use in patients treated per protocol by logistic regression analysis.

Results: 66 (36F) patients were randomised to treatment and 53 completed the study. 6 patients withdrew due to severe exacerbations of UC (2 placebo, 2 omega-3, and 1 each omega-6 and both groups), 4 withdrew because of side effects (1 each group), and 3 defaulted from follow up. Daily mean prednisolone (\pm SD) for all groups was 19.8 \pm 9.6, 11.4 \pm 9.1, 8.9 \pm 9.3 and 7.2 \pm 8.1mg/d for months 1 to 4 respectively ($p < 0.001$; month 1 to 4). There was no significant difference in mean daily prednisolone requirement in patients treated with omega-3 and omega-6 EFA either alone or together compared with placebo (Table).

	Month 1	Month 2	Month 3	Month 4
Omega-3(14)	16.4 \pm 6.6	11.1 \pm 9.9	9.8 \pm 10.0	7.6 \pm 9.8
Omega-6(13)	21.8 \pm 7.1	13.7 \pm 8.7	8.4 \pm 8.6	7.0 \pm 6.4
Both (13)	21.6 \pm 5.9	12.3 \pm 10.8	9.4 \pm 7.6	7.5 \pm 8.8
Placebo (13)	22.8 \pm 3.5	8.6 \pm 7.3	7.9 \pm 11.0	6.7 \pm 8.0

Similar findings were obtained when results were compared on an intention to treat analysis.

Conclusion: In acute UC we could find no steroid sparing effect with omega-3 or omega-6 EFA supplementation compared with placebo whether given alone or in combination.

W91

MACROSCOPIC AND HISTOLOGICAL INACTIVITY IN ULCERATIVE COLITIS (UC) SURVEILLANCE: A GOOD PROGNOSTIC SIGN?

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Surveillance colonoscopy in UC is imperfect and expensive. Better targeting of especially high and relatively low risk patients would improve its cost-effectiveness. A clinical impression that the risk of neoplasia is lower in those with persistently inactive disease has been tested. Thirteen cases of confirmed dysplasia or carcinoma (n=3) documented between 1/1/93 and 31/12/95 in a major surveillance program, which currently includes more than 400 patients with macroscopically extensive colitis of >10 years duration, were reviewed. For each case, 2 unresected UC controls matched for age, sex, and disease duration were selected from the database. Contemporary records of biennial colonoscopic appearances and the degree of histological activity were compared with those for the patients with neoplasia. At the first occasion of dysplasia/malignancy the cases had had a mean of 23.1 years extensive UC (controls 23.5y), and had undergone 6.8 surveillance colonoscopies (4.9). 58% of colonoscopies in the cases had been reported to show normal appearances or quiescent disease, compared to 78% in the controls (χ^2 : $p < 0.05$). 48% of histological reports in patients with subsequent neoplasia indicated inactive disease, compared to 58% in the controls (not significant). Although persistent macroscopic and histological quiescence of extensive UC may be associated with a lower risk of progression to early dysplasia/malignancy, the magnitude of this effect is unlikely to be sufficient to support a reduced frequency of surveillance colonoscopy.

W90

MUCOSAL AMINOSALICYLATE LEVELS CORRELATE WITH CLINICAL ACTIVITY IN PATIENTS WITH ULCERATIVE COLITIS.

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Introduction Despite maintenance mesalazine treatment some patients with ulcerative colitis relapse frequently. Systemic drug levels do not relate to clinical activity and correlate poorly with tissue levels. We have therefore studied the relationship between rectal tissue drug levels and clinical outcome. **Methods** 20 patients (10 male, age 19-75 years) taking delayed-release mesalazine 2.4g/day were recruited. Each underwent clinical assessment and sigmoidoscopy at 0, 3, and 6 months or at relapse. At each timepoint 24 hour urine collections and rectal biopsies were taken for drug analysis. 9 patients relapsed during the study (reported compliance was good)

Results: mean (sem)	Quiescent throughout n=11	Quiescent but subsequently relapse n=9	During relapse n=9
Mucosal ac5ASA ng/mg	8.2(2.7)	6.2(1.2)	2.3(0.7)
Mucosal 5ASA ng/mg	6.2(1.6)	3.6(1.6)	0.3(0.18)
Urine ac5ASA mg	483(40)	854(178)	557.5(46)
Urine 5ASAmg	79.5(15)	152.7(43)	70.9(15)

Mucosal drug levels were significantly lower at relapse than during quiescent disease (5ASA $p=0.02$, ac5ASA: $p=0.008$). Urinary drug levels were lower but this did not achieve statistical significance. Mucosal 5ASA drug levels were also reduced in patients who were quiescent at entry but who subsequently relapsed ($p=0.02$) whereas total urinary drug levels and ac-5ASA were significantly increased ($p=0.04$), compared to patients who were quiescent throughout. **Conclusion** Mucosal aminosalicilate levels in patients with ulcerative colitis fall appreciably at times of relapse. Patients who subsequently relapse have lower rectal mucosal 5ASA levels and higher urinary drug excretion. This may reflect differences in pharmacokinetics and may predispose to relapse. Rectal mucosal drug analysis is a useful tool in the study of patients with ulcerative colitis.
(Research part funded by Smith Kline Beecham Pharmaceuticals, U.K)

W92

CROHN'S DISEASE PATIENTS IN CLINICAL REMISSION SHOW EVIDENCE OF ONGOING MUCOSAL INFLAMMATION. I Arnett, S Ghosh, H Drummond, A Ferguson. GI Unit, Department of Medicine, University of Edinburgh, Western General Hospital, Edinburgh, Scotland.

Background: Clinical remission in Crohn's Disease is generally defined as a CDAI <150. Endoscopic and histologic disease activities may not correlate. Inflammatory markers in Whole gut lavage fluid (WGLF) such as granulocyte elastase (GE) and IL-1 β have been used as objective measures of both small bowel and colonic mucosal inflammation. We aimed to study whether clinical remission is associated with normalisation of WGLF inflammatory markers. **Methods:** In a prospective study, CDAI was recorded in well characterised CD patients undergoing whole gut lavage with polyethylene glycol electrolyte solution (Klean-Prep®, Norgine), generally as a bowel preparation prior to colonoscopy or barium enema. The first clear fluid passed per rectum was collected, processed by addition of protease inhibitors and stored at -70°C. IL-1 β (normal < 4pg/mL) and IL-8 (normal concentration <20pg/mL) concentrations were measured by ELISA and GE concentration (normal <39nkat/L) was measured by an enzyme-substrate reaction as described previously.

Results: 24 patients with CD were in clinical remission with CDAI <150. 15/24 (62%) of these patients had raised WGLF IL-1 β concentrations, 16/24 (67%) had raised IL-8 concentrations and 7/24 (30%) has raised GE concentrations. Overall,

67% of patients in clinical remission had one or more abnormal WGLF inflammatory parameters.

Conclusion: A significant proportion of CD patients in clinical remission have WGLF features suggestive of ongoing mucosal inflammation. We have previously shown that CD patients with abnormal WGLF inflammatory markers relapse more often than those with normal WGLF parameters. Further research is needed to ascertain whether medical therapy to induce mucosal remission will produce longer relapse free periods

W93

FURTHER VERIFICATION OF THE REALLY USEFUL SIMPLE COLITIS ACTIVITY INDEX.

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Background & Aims: We have devised a clinical scoring system of five simple questions to assess the activity of ulcerative colitis (UC) which correlates significantly with the Powell-Tuck score (1). We have now evaluated the simple clinical score against a complex score devised from clinical and laboratory data (2) as well as biochemical and haematological results relevant to UC (3).

Methods: 60 patients with UC underwent 110 assessments. They completed a questionnaire concerning: bowel frequency (day & night); presence of blood in stool; urgency of defecation; general well being and extracolonic manifestations. Laboratory tests included: haemoglobin; platelet count; haematocrit; erythrocyte sedimentation rate and serum albumin. Scores were calculated as published (1,2) and compared using Pearson correlation.

Results:	Simple Index Correlation with;	r value	p value
	Complex score	0.838	<0.0001
	Albumin	-0.5	<0.0001
	Haemoglobin	-0.322	0.0006
	Platelet count	0.323	0.0006
	Haematocrit	-0.325	0.0005
	ESR	0.321	0.0015

For 8 patients assessed during an exacerbation of their disease the simple score correlated well with the complex score and laboratory parameters.

Conclusion: This simple clinical colitis activity index is a robust tool for assessing the activity of ulcerative colitis.

Ref. (1).RS Walmsley et al. Gut. 1994;35; suppl 5: S29. (2). M Seo et al Am J Gastro. 1992;87;8; 971. (3). W Cooke, P Prior. J Clin Gastroenterol 1984; 6; 17.

W95

PERIPHERAL BLOOD PRO-INFLAMMATORY CYTOKINE PROFILE IN ACTIVE INFLAMMATORY BOWEL DISEASE (IBD) DIFFER BETWEEN SMOKERS AND NON-SMOKERS.

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Strong evidence exists that patients with Crohn's disease (CD) are more likely to be smokers than control population whilst, on the other hand, nicotine improves the condition of patients with active ulcerative colitis (UC). However the mechanism(s) of the effects of nicotine remains elusive. We have investigated whether there are differences in pro-inflammatory cytokines IL-1 β , IL-6, IL-8 between smokers and non-smokers in ex-vivo LPS stimulated blood.

METHODS: 6ml blood were taken from each patient with both active and inactive UC and CD (12 in each group; total n=48) and 12 healthy volunteers (7 patients with UC, 11 with CD and 5 healthy volunteers were smokers). Plasma was separated from 3ml of each blood sample and other 3ml were incubated for 24 h with 20ng/ml LPS before isolating cell free plasma. All cytokines were measured by sandwich ELISA (lower detection limit 15pg/ml). Disease activity was measured by Crohn's disease activity index in CD and Truelove and Witts criteria in UC.

RESULTS: Among patient with IBD LPS stimulated IL-1 β and IL-8 levels among non-smokers were significantly higher than smokers (p<0.05 & P<0.01 respectively). This effect was more pronounced for IL-8 levels particularly among active UC and CD patients (Non-smokers : Smokers; UC (median) 1143 : 684 pg/ml. p<0.001 & CD 954 : 630 pg/ml: p<0.01). IL-6 levels were not significantly different between smokers and non-smokers. IL-1 β and IL-8 levels also correlated well with disease activity (r=0.543 & r=0.64 respectively). In spite of lower cytokine levels, number of monocytes, a primary source of pro-inflammatory cytokines, was higher among smokers (p < 0.001).

CONCLUSIONS: 1. Non-smokers tend to have higher levels of pro-inflammatory cytokines than smokers.

2. These results indicate one possible way (probably a cytostatic activity) by which nicotine is effective among active UC patients.

W94

MESENTERIC MARGINAL ULCERATION IN CROHN'S DISEASE: CORRELATION WITH VASCULAR ANATOMY AND CRITICALLY-PERFUSED SITES. A Anthony, RE Pounder, AJ Wakefield, AP Dhillon. *Inflammatory Bowel Disease Study Group*, Depts of Histopathology/Medicine, Royal Free Hospital, London, UK.

Background/Aim. In Crohn's disease (CD) of the ileum, ulcers lie along the same side of the bowel as the mesenteric attachment (ie. mesenteric margin), while the anti-mesenteric mucosa is often spared. The mesenteric and anti-mesenteric borders of the human small intestine are supplied respectively by *vasa brevia* (VB) and *vasa recta* (VR) feeding vessels. CD affects the terminal ileum more often than the jejunum. It has been proposed that mucosal infarction, as a consequence of primary granulomatous vasculitis, contributes to CD. We tested the hypothesis that CD ulcers along the ileal mesenteric margin are explained by the existence of VB end arteries within the human ileum but not the jejunum. **Methods.** Post mortem specimens of normal terminal ileum and jejunum were dissected from adult cadavers (n=8). Mesenteric arcade arteries were cannulated and perfused with carbon (India) ink with or without prior ligation of single isolated VR or VB. Specimens were fixed and cleared by Spalteholz's method. The blood supply of the bowel wall and the submucosal plexus was examined by dissection microscopy. Tissues were also examined histologically.

Results. The submucosal vascular plexus of the jejunum was more extensive than that of the terminal ileum. The submucosal vascular plexus derived from ileal VB were noted to be end-arteries with little or no communication with the submucosal plexus formed from VR. Ligation of both isolated ileal and jejunal VR prior to carbon ink perfusion did not affect filling of the submucosal plexus. Prior ligation of ileal, but not jejunal, VB revealed filling defects of the submucosal plexus along the mesenteric margin. **Conclusion.** In the ileum, VB do not communicate with the main submucosal plexus, (ie. they are end arteries) suggesting that pathological occlusion of ileal VB would preferentially render ischaemic, areas of the ileum along the mesenteric margin. These findings support a vascular hypothesis for CD and may explain the ileal and mesenteric distribution of CD ulcers.

W96

DIFFERENTIAL EFFECT OF STEROIDS ON NITRIC OXIDE (NO) PRODUCTION BY CYTOKINE STIMULATED HT-29 CELLS. Dr JD Linshan, Dr G Kofos, Dr DAF Robertson, Professor J Westwick. Dept of Pharmacology & Pharmacy University of Bath

Background. Studies in colitis have shown increases in NO production and increased inducible NO synthase activity in the inflamed mucosa, especially in colonic epithelial cells. We have shown that the colonic epithelial cell line HT-29 produces NO in large quantities when stimulated with a mixture of the cytokines TNF- α (100ng/ml), IL-1 α (10ng/ml) and IFN- γ (300U/ml) and this is inhibited by pre-treatment with IL-13. Steroids are used to treat IBD patients and in respiratory epithelial cells are known to reduce NO production.

Aim. To examine the effect of two steroids, prednisolone and budesonide on the production of NO in a colonic epithelial cell line.

Methods. Growth arrested monolayers of HT-29 were pre-treated for 2 hours with increasing concentrations (0-300nM) of either prednisolone or budesonide dissolved in McCoy's 5A medium. The cells were then stimulated with the above cytokine mix. Media was collected at both 24 (n=4) & 48 (n=4) hours. NO production was measured using a fluorometric assay detecting nitrite.

Results. At 24 hours nitrite concentration increased from 124 \pm 20 (control \pm SEM) to 309 \pm 67nM per 10⁶ cells with cytokine stimulation. Pre-treatment with prednisolone concentrations up to 300nM made no difference to nitrite production. Pre-treatment with budesonide decreased nitrite production at concentrations of 10nM to 182 \pm 55, 30nM to 196 \pm 36, 100nM to 190 \pm 28 and 300nM to 203 \pm 34 nM per 10⁶ cells.

At 48 hours nitrite concentration increased from 211 \pm 28 (control \pm SEM) to 534 \pm 121nM per 10⁶ cells with cytokine stimulation. Pre-treatment with prednisolone concentrations up to 300nM made no difference to nitrite production. Pre-treatment with budesonide decreased nitrite production at concentrations of 30nM to 370 \pm 81, 100nM to 347 \pm 89 and 300nM to 273 \pm 24 nM per 10⁶ cells.

Conclusion. Pre-treatment with budesonide but not prednisolone at comparatively high concentrations decreases the production of nitrite by HT-29 cells at both 24 & 48 hours. The beneficial effect of prednisolone in colitis is unlikely to be due to a direct effect on NO production by colonic epithelial cells.

W97

EXPRESSION OF INTEGRIN $\alpha 4\beta 7$ ON CIRCULATING LYMPHOCYTES IN INFLAMMATORY BOWEL DISEASE.

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Background: The cell adhesion molecule integrin $\alpha 4\beta 7$ is involved in the migration of B and T lymphocytes to the gut. Anti- $\alpha 4$ integrin antibodies reduce colonic inflammation in the Cotton-top tamarin.

Aim: To determine if there is any change in the expression of integrin $\alpha 4\beta 7$ on circulating lymphocytes in inflammatory bowel disease patients.

Methods: Peripheral venous lymphocytes from 7 normal controls, 16 Crohn's disease (CD) and 9 ulcerative colitis (UC) patients (both active and inactive disease) were studied using flow cytometry. The percentage of lymphocytes expressing integrin $\alpha 4\beta 7$ was determined using monoclonal antibody Act-1 and an indirect immunofluorescence technique. The relative number of $\alpha 4\beta 7$ receptors per lymphocyte was compared by calibrating the mean fluorescence intensity (MFI) in fluorescence (MEF) units for each population of $\alpha 4\beta 7^+$ lymphocytes.

Results	Mean percent $\alpha 4\beta 7^+$ lymphocytes \pm SEM	MFI of $\alpha 4\beta 7^+$ lymphocytes \pm SEM
Controls	71.9 \pm 5.3	2816 \pm 419
CD Active	69.1 \pm 3.5	3614 \pm 313
Inactive	77.3 \pm 3.8	2810 \pm 524
UC Active	68.2 \pm 5.8	2624 \pm 234
Inactive	82.0 \pm 2.3	2799 \pm 441

No significant difference in values ($p > 0.084$) between any disease group and control group, or between any two disease groups.

Conclusion: In inflammatory bowel disease, mucosal accumulation of lymphocytes is not associated with a change in the proportion of circulating lymphocytes expressing the gut homing integrin $\alpha 4\beta 7$, or in the relative density of lymphocyte $\alpha 4\beta 7$ receptors. However, anti- $\alpha 4\beta 7$ therapy may be beneficial in treating inflammation by reducing the proportion of lymphocytes recirculating through the gut.

W99

ABSENCE OF *E. COLI*, *LISTERIA* AND *KLEBSIELLA PNEUMONIAE* ANTIGENS WITHIN INFLAMMATORY BOWEL DISEASE TISSUES.

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Background & Aims: Colonic bacteria may have a major role in the pathology of inflammatory bowel disease (IBD). *E. coli*, *Listeria* and *Streptococcal* antigens have been found in the inflamed bowel wall of French families with IBD (Yui et al, *Gastroenterology* 1995;108:1396) and serum antibodies to a number of organisms including *Klebsiella pneumoniae* and *E. coli* occur in IBD. We therefore undertook an investigation for persistent microbial antigens within IBD affected tissues.

Methods: Formalin-fixed and paraffin-processed sections from resected bowel specimens of 53 patients (19 ulcerative colitis [UC], one with AS; 23 Crohn's disease [CD]; 11 normal tissues from cancer resections) were investigated. Control tissue consisted of normal human small bowel injected submucosally with *E. coli*, *Listeria Monocytogenes* NCTC 7973, *Proteus mirabilis* and *Klebsiella pneumoniae* serotypes K2,3,17,21,26,36 and 50, along with colonic biopsies from a child with *E. coli* 0114 infection. Sections underwent Gram-Twort and specific immunohistochemical staining with antibodies for *E. coli* (DAKO B357), *L. Monocytogenes* (DIFCO 2302-50) and *K. pneumoniae* (Biogenesis 5580-5208 and Sanbio-Monosan 2006), using an immuno-peroxidase technique (DAKO Duet).

Results: *E. coli*; positive staining on luminal surface, including ulcers in 41% of UC, CD and normals. *Listeria Monocytogenes*; two cases (both Crohn's disease) showed positive staining confined to mucus layer. *Klebsiella pneumoniae*; superficial staining in 14% (4 CD, 2 UC, 2 normal) of patients.

Conclusion; Microbial antigens of *E. coli*, *Listeria monocytogenes* and *Klebsiella pneumoniae* are found only on the epithelial surface and not within the affected tissues in inflammatory bowel disease.

W98

THE IMMUNE RESPONSE TO *KLEBSIELLA PNEUMONIAE* IN INFLAMMATORY BOWEL DISEASE AND ANKYLOSING SPONDYLITIS.

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Background: Occult bowel inflammation is found in up to two thirds of ankylosing spondylitis (AS) patients. IgA antibodies to *Klebsiella pneumoniae* (*Kleb.p*) are implicated in the pathogenesis of AS in HLA-B27 positive patients and have been found in inflammatory bowel disease (IBD). It has been suggested that the important serotypes of *Kleb.p* in AS are K26, 36 and 50. The serotypes involved in IBD are unknown. **Aims:** To define the antibody subclass response and *Kleb.p* serotypes involved in IBD and AS. **Methods:** Sera was studied from HLA-B27 positive AS patients (40), Crohn's disease [CD] (46), ulcerative colitis [UC] (38), coeliac disease (50) and normal blood donors (40). Direct, Ig subclass-specific ELISAs were performed using whole bacterial and capsular extracts of *Kleb.p* serotypes K2,3,17,21,26,36 and 50. Mean ODs were compared using Student's t-test, significance was taken as $p < 0.02$. **Results:** Significantly raised antibodies compared with normal controls were found in: AS; IgG to capsular extracts of K2,3,21,36,50 and whole bacterial preps. of K36,50; IgA to capsular K2,3,17,21,26,36,50 and whole bacteria K21,26,36,50. CD: IgG and IgA to capsular extracts of all serotypes; IgG to whole bacteria K17; IgA to whole bacteria K17,21,26,36,50. IgM to capsular and whole bacteria of all serotypes; UC; IgG to capsular K17,36,50 and whole bacteria K3,50; IgA to capsular extracts K2,3; *Coeliac disease*; no elevation.

Conclusion; A broad range of *Kleb.p* capsular serotypes are involved in the immune response to *Kleb.p* in AS, CD and UC. The similarity of immune response between IBD and AS is further evidence of the common association of gut and joint inflammation.

W100

SMOKING AND APPENDICECTOMY IN TWINS DISCORDANT FOR INFLAMMATORY BOWEL DISEASE (IBD).

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These factors have been shown to either be protective (e.g. smoking & appendicectomy in ulcerative colitis (UC)), or a risk (e.g. smoking in Crohn's disease (CD)), for the development of IBD. Potential confounders include material and cultural circumstances in childhood. An unaffected co-twin provides an ideal control, minimizing random and "false" systematic differences in these confounders. In addition a twin also controls for genetic susceptibility. Finally the timing of the exposures, in relationship to the disease onset, is critical to their assessment as "true" risk factors. A twin case-control method was used to study these factors. **Method:** A UK registry of 175 twins-pairs, at least one of which had IBD, was validated for disease status and zygosity. Each member was sent, sequentially, questionnaires asking about childhood events and smoking (Q1) and other life events including appendicectomy (Q2). **Results:**

Of the 110 same-sex discordant pairs in the registry both twins in 88 pairs replied to Q1 (80%), and in 67 pairs to Q2 (79%).

Risk factors	Case	Control	Odds Ratio	Significance
Smoking ever				
Crohn's disease	24	17	2.5	$p=0.18$
ulcerative colitis	18	19	0.8	$p=1.00$
Smoking before Diagnosis				
Crohn's disease	21	14	2.5	$p=0.18$
ulcerative colitis	17	18	0.6	$p=0.72$
Appendicectomy				
ever	9	6	1.6	$p=0.57$
before diagnosis	3	6	0.5	$p=0.48$
Appendicitis	0	5		$p=0.057$

Though no exposure achieved significance, the trend in smoking was similar to that previously reported for the UC and CD. There were no cases of appendicitis among the twins with IBD, this despite very similar environmental exposures (assessed by sharing a bedroom, classes, hobbies and time together) to their twins who developed appendicitis.

Conclusion: Differences in exposures in twin studies are more noteworthy because of the very close matching of case and control. Though no factor achieved significance, the relationship of appendicitis to IBD seems worthy of further study.

W101

INVESTIGATION OF PLATELET-ACTIVATING FACTOR-INDUCED SECRETION IN HUMAN COLON. R.A. Borman, R. Jewell, K. Hillier, Clinical Pharmacology Group, Biomedical Sciences, University of Southampton, Southampton SO16 7PX, UK.

Platelet-activating factor (PAF) has been implicated as a putative mediator of the diarrhoea associated with inflammatory bowel disease (IBD), endotoxic shock, and cholera. Increased levels of PAF have been found in specimens of human colon taken from patients with IBD, and when culture medium bathing such specimens is applied to rat colon, there is a significant increase in fluid secretion across the mucosa. In addition, it has been shown that exogenously-applied PAF enhances fluid secretion in rat colon. The aim of the present study was to determine whether PAF exerts pro-secretory actions in human colon, and to investigate the mechanism of action.

Segments of human sigmoid colon were obtained from specimens removed at operations for carcinoma. After removal of smooth muscle, sheets of mucosa complete with submucosa were mounted in Ussing chambers for measurement of short-circuit current (I_{sc} ; an indicator of electrogenic fluid secretion). Tissues were exposed to varying concentrations of PAF, and responses modified by a selection of inhibitors.

Serosal application of PAF (10^{-9} to 10^{-5} M) induced a significant increase in I_{sc} across human sigmoid colonic mucosa, with a maximum response of $74.3 \pm 9.5 \mu A cm^{-2}$ at 10^{-5} M and an EC_{50} of 18.2 nM (n=6). Mucosal application of PAF (10^{-6} M) had no effect on I_{sc} (n=6). Prior treatment of tissues with indomethacin (1 μ M, n=4) or WEB 2170 (a PAF receptor antagonist, 10 μ M, n=4) significantly reduced the secretory response to PAF, signifying the response is mediated via a specific PAF receptor and dependent on a product of cyclo-oxygenase enzymes. In addition, application of the loop diuretic bumetanide (10^{-8} to 10^{-5} M, an inhibitor of chloride ion secretion) caused a concentration-dependent inhibition of the secretory response to PAF (n=3).

In conclusion, application of PAF induces significant fluid secretion across human colonic mucosa. The response is dependent on a specific PAF receptor and cyclo-oxygenase products. The rise in I_{sc} can be accounted for by an increase in chloride ion secretion.

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W103

LOW TISSUE ENDOTHELIN LEVELS IN INFLAMMATORY BOWEL DISEASE, DESPITE ENHANCED ET-2 GENE EXPRESSION S.A. McCartney, *T.D. Warner, *M. Woods, P.D. Fairclough, M.J.G. Farthing. Digestive Diseases Research Centre and *The William Harvey Research Institute, St Bartholomew's and the Royal London School of Medicine and Dentistry. London U.K.

Endothelins (ETs) are implicated in the pathophysiology of inflammatory bowel disease (IBD). ETs are produced by inflammatory, endothelial and epithelial cells in response to stimulation from cytokines (eg TNF- α , IL-1 and IL-2). ETs stimulate further cytokine and prostanoid production and cause local ischaemia and increased vascular permeability. We have assessed the tissue content of ETs by sandwich ELISA and expression of mRNA for the preproendothelins 1, 2 and 3, ET_A and ET_B endothelin receptors in patients with active, treated and quiescent IBD. Biopsy or resection material was obtained from 55 patients: 21 with Crohn's disease, 18 with ulcerative colitis and 16 controls. Samples were snap frozen and stored at $-70^\circ C$. $ET_{1/2}$ was measured in 45 samples and RT-PCR for mRNA for preproET-1, 2 and 3, ET_A and ET_B receptors and GAPDH was performed on 54 samples.

There was significantly less $ET_{1/2}$ in UC and Crohn's vs. controls: UC 15.3 ± 4 pg/mg vs. 25.4 ± 2.8 ($P < 0.03$, Mann Whitney); CD 13.4 ± 2.2 ($P = 0.0035$). No significant differences were seen between subgroups on or off therapy, quiescent or active. RT-PCR for preproET-2 showed that message was present in 40% of control specimens, 81% of CD samples ($P < 0.02$) and 72% of UC samples ($P < 0.06$). PreproET-1 was present in $< 15\%$ of all samples and preproET-3 was virtually absent in all. All patients with active CD were positive for preproET-2 (n=17). ET_A receptors were upregulated in association with preproET-2, and mRNA was present in 43% of controls, 79% with CD ($P < 0.03$) and 71% of UC samples ($P < 0.12$). mRNA for ET_B receptors was less prevalent than that for ET_A but in similar proportions.

Conclusions: Colonic mucosa from patients with IBD contains a reduced quantity of ETs, contrary to previous evidence. This is in contrast to increased mRNA for preproET-2 and ET_A receptors. This disparity may be due to enhanced gene expression matched by increased protease activity in inflamed tissue degrading unbound ET. Interestingly it appears that ET-2, not ET-1, is the physiologically significant isopeptide within the human colon.

W102

STONE INHIBITOR/PROMOTOR RATIO, A RISK FACTOR FOR RENAL CALCIUM OXALATE CALCULI FORMATION IN INFLAMMATORY BOWEL DISEASE - N. McConnell, S. Campbell, I. Gillanders, H. Rolton and B.J. Danesh. Biochemistry and Gastroenterology Departments, Stobhill NHS Trust, Glasgow, G21 3UW, U.K.

INTRODUCTION: Enteric hyperoxaluria has traditionally been seen as the cause of the higher incidence of calcium oxalate renal stones in inflammatory bowel disease and malabsorption syndromes compared to the general population. This study was undertaken to examine urinary factors contributing to this increased risk.

METHODS: Forty patients with inflammatory bowel disease (IBD) were studied along with 17 healthy controls. Two of 25 patients with Crohn's disease had stones confirmed (8%), a further 5 (20%) had a history of renal stone symptoms. None of the 15 patients with ulcerative colitis (UC) had either stones present or a history of renal stone symptoms. Levels of oxalate and calcium (known stone promoters), and citrate and magnesium (known stone inhibitors) were measured in 24 hour urine collections.

RESULTS: Hyperoxaluria was present in 36% of Crohn's patients but none of the UC group. Renal calculi or history of stone symptoms were no more common in hyperoxaluric Crohn's patients than in those with normal urinary oxalate output indicating urinary oxalate levels are less important in stone development than previously suggested. Crohn's patients had significantly lower urinary magnesium and citrate outputs compared to both the control and UC groups. In this study a combined deficiency of urinary magnesium and citrate relative to urinary calcium, as expressed in a Cit x Mg/Ca index (CMC), correlated well with apparent risk of renal calculi. Risk of developing nephrolithiasis was higher in Crohn's disease compared to UC and was highest in Crohn's patients following gastrointestinal surgery.

CONCLUSION: In Crohn's disease a low stone inhibitor/promoter ratio seems to be a precondition of stone formation, whereas hyperoxaluria is not, and urinary magnesium depletion may be the critical abnormality in these patients. Avoiding magnesium depletion and correcting inhibitor status by citrate replacement may be a more successful strategy for stone prevention in IBD, using the CMC index.

W104

LOW BONE MINERAL DENSITY IS RELATED TO DISEASE DURATION IN CROHN'S DISEASE AND TO GLUCOCORTICOID TREATMENT AND MALE GENDER IN ULCERATIVE COLITIS. S. Ardizzone, S. Bollani, P. Bettica* P. Molteni, M. Bevilacqua*, G. Bianchi Porro. Departments of Gastroenterology and *Endocrinology, University-Hospital "L. Sacco", Milan, Italy.

Low bone mineral density has been shown in inflammatory bowel disease (IBD), but it is not clear, whether, this bone complication is the same in Crohn's disease (CD) and in ulcerative colitis (UC). In this cross sectional study we evaluated spine and femoral neck bone mineral density (BMD), (expressed as t score), calciotropic hormones (PTH, 25(OH)D, 1,25(OH)2D) and biochemical markers of bone turnover (osteo-calcin, OC; total alkaline phosphatase, ALP; type I collagen C-terminal telopeptide, ICTP) in 51 CD (30 women, 21 men) and 40 UC (15 women, 25 men) patients. Thirty healthy subjects were selected as age-matched controls (C). The two IBD groups were similar for: age (CD=38.7 \pm 13.2 years, UC=34.4 \pm 12.5), disease duration (CD=83.5 \pm 67.7 months, UC=70.9 \pm 44.0) and cumulative prednisolone dose (CPD) (CD=6.16 \pm 5.54 g, UC=6.87 \pm 5.84). Spine and femur t scores were similar in the two groups (spine: CD=1.49 \pm 1.46; UC=1.67 \pm 1.13; femur: CD=1.89 \pm 1.36; UC=1.60 \pm 1.03). Based upon the WHO guidelines, only 8% of CD patients and 15% of UC patients had a normal BMD, 55% (CD) and 67% (UC) were osteopenic, and 37% (CD) and 18% (UC) were osteoporotic. The distribution among the 3 different diagnostic groups was not significantly different between CD and UC groups ($p=0.11$). PTH and 25(OH)2D concentrations were not significantly different among IBD patients and controls. However, 1,25(OH)D concentrations were significantly lower in CD and UC patients compared to controls (CD=28.7 \pm 8.6, CU=28.7 \pm 9.4, C = 34.6 \pm 11.4, $p < 0.05$). Bone turnover was increased in UC patients, but not in CD patients, as shown by significantly increased concentrations in UC patients of both OC (CD=7.77 \pm 5.06, UC=10.03 \pm 6.24, C=6.58 \pm 2.87, $p < 0.05$ vs C) and ICTP (CD=5.74 \pm 3.94, UC=10.28 \pm 4.7, C = 3.48 \pm 0.95, $p < 0.05$ vs CD and C). In a stepwise regression that included age, sex, disease duration and CPD as independent variables, the femur t score was significantly inversely related to disease duration ($r^2 = 0.125$, $F = 6.06$) in CD patients. In UC patients, the spine t score was inversely related to age ($r^2 = 0.107$, $F = 5.49$), and was significantly related to sex, and was more negative in males ($r^2 = 0.3$, $F = 16.1$); the femur t score was significantly related to sex (more negative in males) and inversely related to the CPD ($r^2 = 0.283$, $F = 7.3$). In conclusion, our data show that IBD patients have a diffuse osteopenia whose degree is not different in CD and UC; however, bone turnover is significantly higher in UC. Finally, osteopenia is related to disease duration in CD, while it is related to maleness and glucocorticoid treatment in UC.

Inflammatory bowel disease TH105-TH112

TH105

INDUCIBLE NOS (iNOS) IS EXPRESSED IN THE NORMAL HUMAN COLON

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Background

It is suggested that the expression of inducible Nitric Oxide Synthase (iNOS) is inflammation-dependent in the human colon. Hitherto, the expression of iNOS has only been demonstrated in the inflamed human colon. We investigated iNOS expression in both acutely inflamed and normal colonic tissue.

Materials and Methods

Colectomy specimens from patients with active ulcerative colitis (n=8) and histologically normal tissue from patients undergoing resection for colorectal carcinoma (n=8) were studied. Tissue was immediately frozen in liquid nitrogen and post-fixed as required. RT-PCR using specific iNOS primers giving a 423bp product and standard western blotting were performed on fresh, frozen tissue to evaluate expression of iNOS. Cellular localisation of iNOS protein was established using ABC immunohistochemistry with a monospecific iNOS antibody (Santa Cruz). Paraffin-embedded, diseased (n=6) and normal (n=6) colonoscopic and sigmoidoscopic biopsies were evaluated for iNOS localisation to exclude the possibility that iNOS expression was secondary to surgical manipulation.

Results

iNOS mRNA and protein was expressed in all specimens. Irrespective of the means by which tissue was obtained, labelling of iNOS was seen not only in diseased but also in normal tissue in both epithelial and inflammatory cells of the lamina propria. This staining was neutralised when the antibody was pre-absorbed with iNOS peptide illustrating specific iNOS localisation.

Conclusion

These results suggest that iNOS is expressed in the epithelium of normal colon in addition to that of ulcerative colitis. It may have an, as yet, undetermined physiological role.

TH106

MECHANISMS FOR DETOXIFYING HYDROGEN SULPHIDE IN THE GASTROINTESTINAL TRACT

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Hydrogen sulphide (H₂S) is synthesised mainly by sulphate reducing bacteria in the large bowel. The mechanisms by which this highly toxic gas is detoxicated thus preventing mucosal injury are poorly understood. The microsomal enzyme thiol methyltransferase (TMT) is able to detoxify H₂S by methylation. The mitochondrial enzyme rhodanese is also able to detoxify H₂S by conversion to thiocyanate. We have sought activity for TMT and rhodanese in the human gastrointestinal tract. In addition, as a control, we have determined activity of the cytosolic enzyme thiol purine methyltransferase (TPMT). This enzyme methylates sulphhydryl groups on aromatic compounds e.g. 6-mercaptopurine, but is not able to detoxify H₂S.

Mucosa was obtained from surgery. TMT assay was performed using β mercaptoethanol as the methyl acceptor and co-factor, tritium labelled S-adenosyl methionine. TPMT assay was performed using 6-mercaptopurine as the methyl acceptor. Rhodanese activity was determined by measuring thiocyanate production from thiosulphate and cyanide

	Oesop hagus	Stomach	Small intest.	Right Colon	Left Colon	Rectum
n	4	5	2	5	12	7
TMTx10 ³	4(1)	43(13)	91(12)	87(11)	50(9)	51(6)
Rhodanese	16(6)	34(11)	68(32)	129(38)	112(19)	110(18)
TPMTx10 ³	12(3)	26(9)	36(4)	33(6)	28(4)	30(3)

The Table shows mean(SEM) pmol/min/ug enzyme activity. Activity of TMT and rhodanese was highest in the large bowel, with lowest levels in oesophagus. In contrast TPMT activity was highest in the stomach. The distribution and activity of enzymes detoxifying H₂S may be important in ulcerative colitis or large bowel cancer, where chronic mucosal injury by H₂S may play a pathogenic role.

TH107

THE CONTRIBUTION OF DIETARY PROTEIN FROM MEAT TO FAECAL SULPHIDE EXCRETION.

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Aim: To determine the effect of consuming diets differing in meat content on concentration of faecal sulphide (mmol/g wet weight).

Background: The dissimilation of inorganic sulphur compounds (SO₄, SO₃ etc.) by sulphate-reducing bacteria (SRB) and by the fermentation of sulphur amino acids produces hydrogen sulphide (HS⁻) within the colonic lumen. HS⁻ is a cell poison and is toxic to the colonic epithelium by inhibition of β-oxidation of butyrate. In a study of the effect of dietary sulphate on SRB activity in ulcerative colitis (UC) patients, alterations in dietary sulphate intake affected sulphide production in the colon (Pitcher et al., 1996). This study investigates the contribution of sulphur amino acids in the diet to generation of sulphide in the colon.

Methods: Six healthy, male volunteers were maintained in a metabolic suite and fed a sequence of five randomised diets, varying in meat content only (0g, 60g, 240g, 420g and 600g/day). The duration of each test period was ten days. On days 9 and 10 of each period, faecal and urine samples were collected for the measurement of sulphide and sulphate respectively. Faecal HS⁻ concentrations were measured by the adapted methylene blue method (Florin, 1991) and total urinary sulphate was measured by ion exchange chromatography (Florin et al., 1991).

Results: Mean faecal sulphide concentrations for the diets containing 0g/day, 60g/day, 240g/day, 420g/day and 600g/day respectively were as follows: 0.216 mmol/g wet weight (+/- 0.13); 0.268 mmol/g wet weight (+/- 0.17); 1.09 mmol/g wet weight (+/- 0.83); 0.72 mmol/g wet weight (+/- 0.54) and 2.78 mmol/g wet weight (+/- 1.63). Mean total urinary sulphates increased from 21.5 mmol/day on the 0g/day diet to 45.8 mmol/day on the 600g/day diet (60g/day- 22.5 mmol/day; 240g/day- 26.5mmol/day; 420g/day- 41.8 mmol/day).

Conclusions: Faecal sulphide excretion increased with increased meat consumption, in a dose response manner except for the 420g/day period. Intake of meat provides an important source of sulphur containing amino acids and may have implications for HS⁻ production in UC. Further work is being carried out to investigate the effects of other sulphur compounds on HS⁻ production in the human colon. Pitcher, M.C.L., Magee, E.A.M., Beatty, E.R. and Cummings, J.H., (1996), Gastroenterology, 110: A992. Florin, T.H.J., (1991), Clin. Chim. Acta., 196: 127-134. Florin, T.H.J., Neale, G., Gibson, G.R., Christl, S.U. and Cummings, J.H., (1991), Gut, 32: 766-773.

TH108

GROWTH FAILURE IN INFLAMMATORY BOWEL DISEASE.

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Growth failure is the most common extraintestinal complication of Crohn's disease (CD) and ulcerative colitis (UC) in children and adolescents. Here we present interim data (at age 18 yrs) from a prospective study of growth in 67 children and adolescents with IBD (52 CD and 15 UC). The difference between observed and expected midparental height (MPH) was related to diagnosis, duration of disease and site of disease.

Results

Crohn's disease	Colonic disease only	Large + small bowel	Small bowel only	Ileocaecal
Height - MPH/cm	-0.35	-5.8	-7.1	-5.2
Mean (95% CI)	(-5.6/4.9)	(-9.9/-2.5)	(-11.9/-2.5)	(-10.1/-0.3)
Mean age at diagnosis (Range)	12.2 (7 - 15)	9.8 (4 - 13)	13 (11 - 17)	11.5 (7 - 16)
n	13	19	9	11
Ulcerative colitis	Pancolitis	Distal		
Height - MPH/cm	-4.5	-0.06		
Mean (95% CI)	(-10.7/1.7)	(-14.2/1.4)		
Mean age at diagnosis (Range)	10.8 (7 - 13)	10.2 (2.5-18)		
n	12	3		

71% of patients with early onset CD and 60% with UC fail to meet their expected heights by 18 yrs, except for CD patients with disease restricted to the colon. Patients with small bowel disease alone were most severely affected, despite having a shorter duration of disease than those with combined small bowel and colonic disease. There was a trend for disease duration to relate positively to growth deficit (< 5 yrs of disease: mean deficit -2.5cm vs. > 8 yrs of disease -6.8 cm). Failure to achieve optimal linear growth in IBD is common and is related to site of disease and probably age of onset.

TH109

LOSS OF BONE MASS IN INFLAMMATORY BOWEL DISEASE (IBD) PATIENTS ON LONG TERM STEROIDS, IS THERE A SAFE LIMIT? M.F.M. Santog^{1,2}, R.J. Erdtsieck¹, M.van Blankenstein².
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The aim of this study was to establish the effect of total life time steroid dosage (TLSD) on bone mass in IBD patients on ongoing or previous steroid treatment. The TLSD was calculated for each patient at their first bone mass measurement, performed to monitor the effects of steroid treatment.

Bone mass was measured by means of dual energy x-ray absorptiometry (DXA) in the lumbar spine and the femoral neck and with single photon absorptiometry in the proximal and distal forearm. The obtained data were compared with a normative Dutch population and transformed into Z-scores (number of S.D. from zero), corrected for age, sex and menopausal state.

128 patients were assessed, 118 of whom had received long term steroids without prophylactic supplements. 92 had Crohn's disease, 36 ulcerative colitis. The mean duration of steroid therapy was 102 months (\pm 6 months SEM), and the mean daily prednisone dose was 13 mg (\pm 0.7 mg). Bone mineral densities (BMD), measured at the spine (L₂-L₄), the femoral neck, the trochanteric region, the proximal and distal forearm were -.84, -.75, -.83, -.31 and -.61 respectively. Except for the BMD in the proximal forearm, all sites were significantly reduced (P<.01). A significant negative correlation was observed between BMD at the various sites, the TLSD and the duration of steroid treatment, especially when exceeding 100 months. A decrease of BMD > 1 SD was only found in patients with a TLSD > 7.5 gram prednisone. BMD was not influenced by the type of IBD, the duration of the disease and the number or nature of resections.

Conclusions: 1. Bone mass loss in IBD is related to TLSD and the duration of steroid treatment. 2. The upper limit of a relatively safe TLSD seems to be about 7.5 gram prednisone. 3. Above this limit patients should be monitored by regular BMD measurements.

TH111

HYBRID CAPTURE FOLLOWED BY RT-PCR DOES NOT DETECT MEASLES RNA IN INTESTINAL TISSUE

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Aims. The aim of this study was to use a sensitive and robust method of measles RNA detection to search for measles RNA in inflammatory bowel disease (IBD) and intestinal control tissues. Recent epidemiological and immunohistochemical studies have indicated a possible link between measles virus and IBD.

Methods. Two measles nucleoprotein (N) gene RNA transcripts, derived from a recombinant plasmid vector and a modified version of the same, were used to spike tissue homogenates. The first transcript was used to determine the detection limit sensitivity for the method to be employed, and the second, modified transcript was used as an internal positive control. This second, modified transcript yielded a product, after reverse transcription followed by the polymerase chain reaction (RT-PCR), which was larger than the wild-type, non-modified form to allow its discrimination after agarose gel electrophoresis. In experiments to determine the presence of measles virus in IBD, fresh frozen resection tissue from patients with Crohn's disease (n=10), ulcerative colitis (n=3) and non-IBD control patients (n=7) were homogenised in 2ml of total RNA isolation reagent (Advanced Biotechnologies Ltd.). Duplicate homogenates were spiked with 10⁷ copies of the internal control transcript prior to RNA extraction. Hybrid capture, using measles-specific oligonucleotides linked to paramagnetic supports was performed on extracted RNA. 5ul of hybrid capture eluant was used for measles RT-PCR using r7th DNA polymerase and EZ buffer (Perkin Elmer). Products were electrophoresed and analysed by Southern hybridisation using an internal probe. Extracted RNA was also used for RT-PCR of a housekeeping mRNA species (mRNA of the splicing U1A subunit) to assess RNA quality.

Results. Hybrid capture increased the detection sensitivity by 100-fold over RT-PCR. As few as 10⁴ transcripts in a tissue homogenate could be detected using this method. All but one sample were U1A mRNA positive and all samples were positive for the internal control transcript after RT-PCR. None of the samples analysed were positive for measles RNA.

Conclusion. No measles RNA could be detected in intestinal tissue, either IBD or control, using the methods described in this experiment.

TH110

CYTOKINE EXPRESSION AND RELAPSE OF ULCERATIVE COLITIS: A PROSPECTIVE STUDY.

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In patients with ulcerative colitis the relationship between cytokine expression and clinical activity remains unclear. We have therefore undertaken a prospective study of 12 patients with ulcerative colitis (8 females, aged 19-76 years). Clinical assessments, sigmoidoscopy and rectal biopsies were undertaken at 0, 3, and 6 months or at relapse and biopsies analysed for cytokine expression. IL-1 β , IL-1receptor antagonist (IL-1RA), IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IFN- γ and TNF- α mRNA were analysed using RT-PCR followed by Southern blotting of the PCR products. IL-1 β and IL-1RA protein was measured by ELISA. 6 patients relapsed during the course of the study. **Results:**

mRNA	Quiescent throughout n=18	Quiescent but subsequently relapse n=12	Prior to relapse	During relapse n=6
IL-8	7/14	7/7	5/5	5/5
IL-2	2/14	1/7	5/5	1/5
IL-6	5/14	3/7	4/5	5/5
IL-15	4/14	1/7	3/5	3/5
IFN- γ	5/14	3/7	2/5	4/5
IL-10	4/14	2/7	4/5	3/5
ELISA mean (sem) pg/mg				
IL-1 β	2.9(1.6)	3(0.7)	31(20)	7(1)
IL-1RA	1160(160)	1100(200)	740(160)	1280(400)
RA/1 β ratio	460(90)	586(176)	80(24)	214(60)

(IL-4, 12, 13, TNF- α mRNA were infrequently expressed). **Conclusions:** All patients in relapse expressed IL-8 and IL-6 and most expressed IFN- γ . Patients who subsequently relapsed were more likely to express IL-8 at times of quiescence (p<.05). IL-2 expression was increased prior to but not during relapse episodes (p<.05) suggesting a possible role in initiating but not perpetuating relapse. IL-1 β protein was increased during relapse (p<.05) compared to quiescent disease. IL-1 RA did not increase during relapse. This imbalance between IL-1 β and IL-1RA may be important in the pathogenesis of relapse.

TH112

LIMITED EXPOSURE OF LEFT COLON TO DAILY DOSED ORAL FORMULATION IN ACTIVE DISTAL ULCERATIVE COLITIS: EXPLANATION OF POOR RESPONSE TO TREATMENT?

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Patients with active left-sided ulcerative colitis (UC) often fail to respond to topically active oral agents such as 5ASA's. We have previously shown by daily dosing of a radiolabelled resin that the distal colon behaves like a conduit in healthy volunteers, containing less material compared to the proximal colon (33 \pm 7 v 66 \pm 7%, Gut 1995; 37: A47). Our aim was to examine the relative distribution in distal UC. **Methods:** On 4 consecutive mornings 10 patients (age 33-67; 6M:4F) with active UC extending to the splenic flexure ingested a Eudragit-coated gelatin capsule containing In111 labelled amberlite resin. Patients were scanned on the 4th morning immediately prior to dosing with X counts, and at 4, 8 & 12h later. The distribution of label in ascending (AC), transverse (TC), descending (DC) and rectosigmoid colon (RS) was expressed as % of total colonic activity. Transit time (TT) through each region was calculated as regional counts + X counts x 24h. Similarly, % daily dose (DD) in each region was regional counts + X counts. **Results:** (mean \pm SEM). Averaging the 4 scans, percentage activity was distributed as follows: AC 54 \pm 4, TC 37 \pm 3, DC 7 \pm 2 & RS 3 \pm 1%. The mean % in the distal colon (DC+RS) was significantly less than in healthy controls [n=10] (9 \pm 3% v 33 \pm 7%, p<.002). Distal colonic TT was shorter in colitics (3.9 \pm 2.1 v 19.3 \pm 3.5h), and resulted in a smaller %DD resident within this area (0.16 \pm 0.09 v 0.81 \pm 0.15 x DD, p<.002). **Conclusions:** Following daily dosing of an enteric coated formulation, only 1/10th of the total activity within the colon lay in the distal segment (DC+RS) in patients with distal colitis. Limited exposure of the inflamed distal colon to topically active oral agents may explain the poor response to treatment.

Liver TH113-TH119

TH113

SAPHENO-PERITONEAL SHUNTING FOR DIURETIC RESISTANT ASCITES. S Ryder, J Doran and R Chamley, Departments of Medicine and Surgery, Queen's Medical Centre, Nottingham, NH7 2UH.

Background. Treatment of diuretic resistant ascites is usually by repeated large volume paracentesis, although this is effective, it does involve repeated hospitalisations and has a significant risk of complications. We have used a surgical anastomosis of the saphenous vein to the peritoneal cavity to provide internal drainage.

Patients and Method. Surgery was undertaken in 8 patients, 6 under GA and 2 under LA. Saphenous vein patency was assessed by doppler ultrasound. A groin incision was made, the saphenous vein isolated and a reversed segment anastomosed to the reflection of the peritoneal cavity below the inguinal ligament. All 8 patients had diuretic resistant ascites and had been treated with at least 4 paracenteses prior to surgery. 5 had alcoholic liver disease, 1 hepatitis B, 1 hepatitis C and 1 Budd-Chiari syndrome. Median follow-up was 15 months.

Results. Successful shunt formation was achieved in 7/8 patients (88%). Frequency of paracentesis was markedly reduced following surgery (mean 1.7 per month to 0.1 per month, $p=0.001$). Diuretic dose was reduced in 7 out of 8 patients and discontinued in 5 patients. Surgery failed in one patient due to infection of the wound site. Two further patients developed wound infections which required antibiotic therapy. No thrombotic or other septic complications occurred. Median hospital stay after shunt formation was 6 days (range 2 to 18). One patient later underwent liver transplantation, three further patients died at 7, 12 and 14 months following shunt creation.

Conclusion. Sapheno-peritoneal shunting is an effective means of treating diuretic resistant ascites. It does not involve insertion of foreign material into the vasculature and may represent an alternative to repeated paracentesis without the risks of thrombosis and infection seen with Le Vein shunts.

TH115

HIGH DOSE URSODEOXYCHOLIC ACID (UDCA) IN PRIMARY SCLEROSING CHOLANGITIS (PSC): RESULTS AFTER TWO YEARS OF A RANDOMISED DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL. SA Mitchell, D Bansi, N Hunt*, J Christie, K Fleming* and R Chapman. Department of Gastroenterology and Nuffield Department of Pathology*, Oxford Radcliffe Hospital, Oxford, UK.

Aim: Previous trials of UDCA therapy in PSC have shown improvements in liver biochemistry but varying changes in liver histology. We report the results after 2 years of a double-blind placebo controlled trial of high dose (20mg/kg/day) UDCA in PSC.

Methods: 24 patients (17 male, mean age 54, range 24-81) were randomised to UDCA (n=12) or placebo (n=12). All patients had a pre-trial liver biopsy and cholangiography. 20 patients had repeat liver biopsy and cholangiography at 2 years. 2 patients were withdrawn from the study, the first after 6 months from the UDCA group due to a dominant stricture which required stenting and the second after 15 months from the placebo group due to recurrent variceal haemorrhage. One patient from the placebo group died from an unrelated cause. Pre- and post-trial liver biopsies were staged and graded using a modified histological activity index (HAI) by two histopathologists.

Results: The two groups did not differ significantly on entry. No improvement in symptoms was recorded. Despite the high dose of UDCA used there were no reported side effects. Significant improvement ($p<0.05$) was observed in the serum levels of ALP (mean 455 vs 779 iu/l) and γ GT (mean 157 vs 377 iu/l) in the UDCA group at 2 years compared with entry levels but changes in the bilirubin and AST were not significant. In the placebo group no significant changes were noted. Liver histology revealed an unchanged or improved HAI score in 9/10 of the UDCA group but a worse score in 5/9 of the placebo group. Disease stage remained unchanged or decreased in 8/10 of the UDCA group but progressed in 5/9 of the placebo group.

Conclusion: High dose UDCA treatment of patients with PSC is well tolerated and associated with a significant improvement in both ALP and γ GT after 2 years. In contrast to our previous trial (Hepatology 1992; 16:92A.) using lower doses of UDCA, the majority of the group treated with high dose UDCA had unchanged or improved inflammation (HAI) scores on liver histology and 4/10 showed regression of the disease stage.

TH114

MATERNAL AND PERINATAL OUTCOME IN SEVERE PREGNANCY-RELATED LIVER DISEASE. SP Pereira, J O'Donohue, J Wendon, Roger Williams. Institute of Liver Studies, King's College Hospital, London SE5 9RS.

Acute fatty liver of pregnancy (AFLP) and the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP), are rare but major complications of the third trimester of pregnancy, with published maternal and perinatal mortality rates of approximately 20%. **Aims:** To review the outcome of a large group of patients with severe liver dysfunction in late pregnancy, treated according to a standard protocol for acute liver failure.

Methods: Over a 10 year period, 46 women (median age 30 yr, range 17-41 yr) with a provisional diagnosis of severe AFLP or HELLP syndrome (median gestational age 35 wk, range 24-40 wk), were transferred to our Liver Failure Unit. **Results:** At admission, 32 patients (73%) were preeclamptic, and 21 (46%) were encephalopathic and/or ventilated. The median INR was 1.6 (range 0.9-3.4) and platelet count $107 (19-409 \times 10^9/l)$. 40 patients (87%) had a raised serum creatinine (median 210 μ M, range 63-758 μ M). The median serum bilirubin concentration was 113 μ M (17-646 μ M), rising to a peak value within 48 h of 153 μ M (19-646 μ M). 32 patients (70%) had clinical features and laboratory values consistent with AFLP, while seven (15%) had HELLP syndrome. In seven other patients, causes of severe liver dysfunction unrelated to AFLP or HELLP syndrome, were found. Infectious complications occurred in 19 of the 39 patients (49%) with AFLP or HELLP syndrome - 17 of whom were in the AFLP group. Major bleeding complications occurred in 12 women (10 with AFLP). Nine required laparotomies for clot evacuation, while one with preeclamptic liver rupture underwent liver transplantation. None of the eight patients who delivered vaginally had bleeding complications. Four of the 32 patients with AFLP (12.5%) had a fatal outcome, with a corresponding perinatal mortality rate of 9%. There were no maternal or perinatal deaths associated with HELLP syndrome. **Conclusions:** In contrast to many previous studies, the results of this large series suggest a relatively favourable maternal and perinatal outcome in severe AFLP and HELLP syndrome.

TH116

PRODUCTION OF ANGIOGENIC AND CHEMOATTRACTANT CHEMOKINES DURING MONOCYTE-HEPATOMA CELL ADHESION.

KJ Simpson, NW Lukacs, H Evanoff, RM Strieter & SL Kunkel (introduced by PC Hayes). Dept of Pathology and Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA 48105.

The aim of this study was to determine if interleukin 8 (IL8), a potent angiogenic chemokine, and macrophage inflammatory protein 1 α (MIP1 α), a powerful chemoattractant for monocytes, are produced during monocyte adhesion with hepatoma cells.

METHODS. Human hepatoma cell lines (HepG2 and SK Hep) were co-cultured with PBMC for 24 hours and chemokine concentration measured by ELISA. Monocytes and hepatocytes were separated in transwell culture plates (Costar) to determine if adhesion was a prerequisite for chemokine production.

RESULTS. Monocytes alone produced little IL8 (1.46 ± 0.42 ng/ml, mean \pm SEM, n=8) and MIP1 α (0.01 ± 0.01 ng/ml, n=8). Hepatoma cells also produced little or no IL8 (HepG2 0.79 ± 0.04 , SK Hep 13.23 ± 3.5 , n=8) and MIP1 α (HepG2 0, SK Hep 0.03 ± 0.01 , n=8). Both IL8 and MIP1 α concentrations significantly increased when monocytes were co-cultured with HepG2 (IL8 19.58 ± 2.5 , MIP1 α 3.64 ± 0.16 , n=8) or SK Hep cells (IL8 362.0 ± 80.8 , MIP1 α 3.48 ± 0.58 , n=8). Separating PBMC from the hepatoma cells, using transwell plates, resulted in significantly reduced concentrations of IL8 (HepG2 5.66 ± 0.43 , SK Hep 47.9 ± 7.7 , n=8) and MIP1 α (HepG2 0.40 ± 0.03 , SK Hep 0.30 ± 0.06 , n=8).

CONCLUSIONS. Production of IL8 and MIP1 occurs during monocyte adhesion with hepatoma cells in an adhesion dependant manner. This may enhance the recruitment of other inflammatory cells to the site of a hepatoma, but may also enhance the growth and metastatic potential of the tumor by promoting angiogenesis.

TH117

PROLIFERATING HEPATOCYTE CELL LINES CONDITION THEIR EXTRACELLULAR ENVIRONMENT WHILST DEVELOPING THREE DIMENSIONAL CONFIGURATION IN A HOLLOW FIBRE CARTRIDGE.

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Introduction: Bioartificial liver support devices must both nourish and detoxify the blood of liver-failure patients. Synthesis and transport of proteins are essential.

Methods: A human hepatocyte cell line, HHY41 (1.5×10^7 cells) was cultured in the extracapillary space (ECS; 1.4 mls) of a hollow fibre cartridge (HFC). Culture medium was recirculated (50 mls/min) through the intracapillary space (ICS) of hollow fibres with 0.5 μ m pores. HFCs with polypropylene (pp) fibres were inoculated with cells attached to microcarriers. HFCs with fibronectin (fn)-coated fibres were inoculated with freshly trypsinised cells. Samples were taken from the medium reservoir for ELISAs to determine albumin, α 1-antitrypsin and fibrinogen. Cultures were terminated after 30-35 days.

Results: Data were similar for cells grown either in the presence of fn-fibres or pp-fibres and microcarriers. Albumin (170-200 μ g/day) and α 1-antitrypsin (210-280 μ g/day) increased continuously during culture. Fibrinogen appeared in the reservoir within 3 days (20-50 μ g) but did not increase until after 16-20 days (60-100 μ g/day).

Cells initially adhered to microcarriers were found to have left the carriers and formed 3-dimensional structures of cells around and between the fibres. Cells grown on fn-fibres had grown around the fibres in multi-layered sheets.

Conclusions: Production of proteins such as albumin and α 1-antitrypsin increased continuously throughout the experiment. Fibrinogen was detectable but did not increase until 16-20 days of culture presumably reflecting fibrin deposition as cells condition their environment. During this time cells adopted multicellular three-dimensional structures whether initially adhered to microcarriers or grown in the presence of fibres coated with fibronectin.

TH119

BENEFICIAL IN VITRO EFFECTS OF TUCARESOL ON THE IMMUNE RESPONSE TO HEPATITIS C VIRUS

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A strong T helper lymphocyte (T_H) response to hepatitis C virus is important for viral clearance, while viral persistence is associated with a weak T_H response. The orally bioavailable drug tucaresol selectively enhances T_H response and to assess its therapeutic potential in HCV infection we investigated the *in vitro* effects of tucaresol on T_H response to HCV proteins.

Method: Peripheral blood mononuclear cells from 18 patients with chronic HCV infection were cultured in the presence or absence of both tucaresol and HCV proteins - NS3 and core. Proliferative response was measured using ³H-thymidine uptake and cytokine production (IL-2, IL-4 and IFN γ) was measured in the culture supernatants using standard ELISA.

Results: Tucaresol enhanced T_H proliferation in 17 of the 18 patients in response to HCV core (mean increase 94%) and in 10 of the 18 to NS3 (mean increase 56%). Tucaresol increased mean IL-2 production in response to HCV core and NS3 (45 to 96 pg/ml, and 42 to 71 pg/ml, respectively). Detectable IL-2 was found in the lymphocyte culture supernatants of all 18 patients in response to NS3 and core whereas IL-4 was found in only 2. In 4 patients background IL-4 production by lymphocytes in the absence of any antigen was found and tucaresol reduced the mean IL-4 in these cases from 46 to 5.8 pg/ml. Low levels of IFN γ were found in response to NS3 and core in 10 of the 18 patients with a rise in mean values from 12-36 pg/ml and 14-37 pg/ml respectively with tucaresol.

Conclusions: Tucaresol favours production of a T_H 1 cytokine profile and enhances lymphocyte response to viral proteins in patients with chronic HCV infection. These results suggest that tucaresol has potential as a new treatment for HCV infection.

TH118

PROGNOSTIC SIGNIFICANCE OF HEPATIC VENOUS PRESSURE MEASUREMENTS IN CIRRHOSIS.

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Introduction: We wished to examine whether portal pressure measurements were predictive of survival in cirrhotic patients, and if there was a height of portal pressure that had prognostic significance.

Method: 132 (81 male, 51 female) cirrhotic patients (Childs A:35, B:5, C:46) who consecutively underwent hepatic venous pressure gradient (HVPG) measurement were investigated. Median age was 52 years. (range 21-79) 63% had alcoholic cirrhosis. Prior to admission, 112 patients had bled from oesophageal varices and 40 patients (30.7%) were on long term treatment for the prevention of rebleeding. Differences in survival curves using an HVPG of 16mmHg were tested using the log-rank test.

Results: 41 patients died during the follow up period (median 550 days). Using multivariate analysis, previous long term endoscopic or surgical treatment ($p=0.03$), prothrombin time ($p=0.005$), ascites ($p=0.0001$) and HVPG ($p=0.001$) were found to be the only significant predictors of survival. Dividing the patients into three groups according to the time of HVPG measurement in relation to a variceal bleeding episode (0-7, 8-14, >15 days) the predictive value of HVPG was found to be much higher if the measurement was taken within the first ($p=0.03$) or second ($p=0.004$) week from bleeding.

Conclusion: HVPG measurement provides further prognostic information in addition to that obtained from the Child-Pugh classification. In patients with a previous variceal bleed, this predictive value is higher if the measurement is taken within two weeks of bleeding. We advocate the routine use of HVPG measurement, not only in the management of bleeding, but also in the general work up of cirrhotic patients.

Oesophagus TH120-TH150

TH120

PSEUDOMEMBRANOUS ESOPHAGITIS (PME). A K Nayyar, C Royston, K.D Bardhan, Rotherham General Hospitals NHS Trust, Rotherham, UK.

Introduction and Aim PME is an uncommon condition of striking endoscopic appearance. Here we describe its features, associated conditions & outcome. **Endoscopic appearance** Concentric slough or membrane covers much of the lower half or the whole of the esophagus, ending abruptly at a normal squamocolumnar junction. Yellow, or black with digested blood, the membrane can be peeled away to reveal fragile esophageal mucosa. These appearances differ markedly from erosive esophagitis. **Histology** The pseudomembrane shows fibrinous exudate, inflammatory cells but no basement membrane (hence "pseudomembranous") and esophagus severe inflammation, granulation & loss of epithelium. Bacteria, fungi & viral inclusions are not identified. **Results Patient numbers** From 1982-May 1996 n=42. **The setting** 36(86%) were in-patients, many already seriously ill. 10 had gastrointestinal (GI) disorders (eg intractable vomiting, diarrhea, malignancy), 9 non-GI (eg stroke, respiratory failure, other malignant disease) and 17 were admitted with GI bleeding. **Indication for endoscopy** GI hemorrhage n=27(64%), dysphagia n=5, pain and/or vomiting n=7, anemia n=2, peptic ulcer follow-up n=1. **Other endoscopic findings** Peptic ulcer n=12; outlet stenosis n=4; dilated stomach but without obstruction n=3. **Demography** Male 26 (62%). Age >65 n=30 (71%); 35-64 n=11(26%). **History of reflux/dyspepsia** Nil n=15(36%); <3wk n=9(21%). **Recent drug usage** 13/42 (31%) had antibiotics and 7/42 (17%) had NSAIDs. **Early outcome** 7 died shortly after diagnosis & 5 were still on healing treatment when the study ended. Most of the other 30 were re-endoscoped after 3 months treatment with cimetidine 1.6g or omeprazole 20mg. The pseudomembrane had cleared in all and the esophagus looked normal. **Long-term outcome** After healing 30 patients were followed (mean 39 months, range 1-139), 22 on maintenance treatment (MT) with cimetidine (mainly 1.6g) or omeprazole (20mg). 26 continue in remission including 8 patients off MT. Despite this treatment 4/22 relapsed, 3 with PME, again associated with serious illness as at presentation. Only one patient developed erosive esophagitis. **Discussion** PME is different from erosive esophagitis and its cause(s) unknown. A possibility is unusual tissue response in the elderly, with underlying serious illnesses, resulting in diffuse esophageal inflammation and sloughing of squamous epithelium. Infectious agents have not been identified. Peptic ulcer, vomiting, antibiotics & NSAIDs may contribute. The role of gastroesophageal reflux in PME is not known. **Conclusion** This probably is the first description of idiopathic PME. The condition is uncommon, of unknown cause, with distinct appearance, associated with severe illness, responds well to treatment, and rarely recurs.

TH121

ALGINATES ALTER OESOPHAGEAL CELL FUNCTION IN AN ANIMAL MODEL. W. Hall, P. E. Ross, D. Hopwood. Dept of Molecular and Cellular Pathology, Ninewells Hospital and Medical School, University of Dundee, Dundee, DD1 9SY.

Background / Aims: Alginates are used to alleviate symptoms of reflux in oesophagus. It has been proposed that they act by forming a barrier to refluxed material. We aimed to develop an animal model to determine whether alginates also play a more complex role by altering cell function.

Methods: Pig oesophageal epithelium was mounted in four Ussing chambers. Fluid phase endocytosis was used as a marker of cell function, therefore the mucosal surface was exposed to a solution containing FITC labelled 0.02µm latex microspheres. In addition 0, 0.001, 0.01 or 0.1µM of alginate A (high m. wt. *Laminaria hyperborea* stem) n=6, B (*Lessonia nigrescens*) n=5, or C (low m. wt. *Laminaria hyperborea* stem) n=5, were added to the four chambers. Tissue was incubated for 1 hr then disaggregated to form single cell suspensions which were examined using flow cytometry. Measurements were made before and after the addition of the quenching agent trypan blue to obtain total and endocytosed fluorescence readings.

Results: Values are % differences compared to no added alginate.

EFFECT ON TOTAL

[ALG]µM	A	B	C
0.001	+ 22%(p<0.05)	none	none
0.01	- 23%(p<0.05)	none	none
0.1	- 23%(p<0.05)	-12% (p<0.1)	+ 63%(p<0.05)

EFFECT ON ENDOCYTOSIS

[ALG]µM	A	B	C
0.001	none	+ 20%(p<0.05)	none
0.01	none	none	none
0.1	none	-27% (p<0.05)	+ 39%(p<0.05)

Conclusions: Depending on their source and structure, alginates are capable of upregulating total or endocytosed fluorescence, indicating changes in cell physiology. At different concentrations the same alginates may also downregulate these.

TH123

FURTHER EVIDENCE THAT SUMATRIPTAN INDUCED CHEST PAIN IS OESOPHAGEAL IN ORIGIN: EFFECT ON OESOPHAGEAL VISCERAL SENSATION. JM Foster, LA Houghton, PJ Whorwell. Dept of Medicine, University Hospital of South Manchester, Manchester, UK.

We have recently suggested that the chest pain experienced by most of the 3-5% of patients taking sumatriptan (S) for migraine is related to oesophageal dysmotility rather than cardiac ischaemia. This is based on our observations that both 16mg and 6mg doses of S alter oesophageal motility without changing the ECG. Furthermore, these changes in motility tended to be greatest in those subjects who experience S-induced chest discomfort compared with those who did not. However, we were unable to show a direct correlation between the time of occurrence of chest discomfort and changes in motility. This could be explained by S affecting the visceral sensitivity of the oesophagus, and it was the purpose of this study to answer this question. Serial balloon distension of the oesophagus was therefore carried out both before and after a subcutaneous injection of 16mg sumatriptan or saline control in 30 normal healthy volunteers (aged 18-34 yrs; 15 male). Treatments were randomised and double blind, and ECG was monitored throughout the studies.

Results	Placebo	Sumatriptan
Volume to discomfort (ml):		
Pre-injection	28(6,30)	29(8,30)
Post-injection	27(10,30)	23(7,30)*
Change pre-post inject*	0(-2,14)	0(-18,6)†
Compliance (ml/mmHg):		
Pre-injection	0.20(0.10,0.35)	0.19(0.11,0.34)
Post-injection	0.19(0.11,0.57)	0.17(0.10,0.30)†
Change pre-post inject*	0.01(-0.13,0.34)	-0.03(-0.08,0.08)†

(Results are expressed as median (range); * p<0.05; † p<0.005)

3 subjects experienced S-induced chest discomfort, but no subject exhibited any ECG abnormalities.

Conclusion Our observation that S increases visceral sensitivity of the oesophagus and reduces its compliance provides further evidence that S-induced chest pain is in most instances oesophageal in origin. Furthermore, it strongly suggests that the role of 5HT₁ receptors should be evaluated in relation to the visceral sensitivity of the gut. "This research was partially funded by GlaxoWellcome, UK."

TH122

CONCENTRATED (80%) ACETIC ACID INGESTION: SYSTEMIC AND GASTROINTESTINAL EFFECTS P.D.Siersema, W.R.Hartmans, J.Dees, and M.van Blankenstein. Department of Gastroenterology, University Hospital Dijkzigt, Rotterdam, The Netherlands.

Ingestion of concentrated (80%) acetic acid (CAA) is a form of suicide practiced by immigrants from Surinam. To compare the effects of CAA ingestion to other caustic agents and to determine if early endoscopy is predictive, data on 132 adult patients (44% M/ 56% F), admitted between 1980 and 1994 for ingestion of a caustic agent, were reviewed. All patients were endoscoped within 24 hours to grade the gastrointestinal lesions (grade 0: none - grade 3: severe). Clinical severity was judged by duration of admission, ICU admission, systemic and local complications.

Results:

Agent (n)	Endosc. grade (%)	Hospitalisation mean (d)	Systemic ICU complic.	Stricture formation	Mortality
CAA (55)	7 18 44 31	7.5	50% ¹ 13 (24%) ¹	4 (7%)	8 (15%) ³
Acid (10)	20 10 30 40	27.0	33% 1(10%)	6 (60%) ²	0
Alkali (67)	20 22 28 30	7.0	25% 1(1.5%)	12 (18%)	2 (3%)

¹CAA vs Alkali: p<0.01; ²Acid vs Alkali and CAA: p<0.01; ³CAA vs Alkali: p<0.05

Systemic complications were only seen in grade 2+3 lesions and included renal damage in 8, liver damage in 9, diffuse intravascular coagulation in 7, and hemolysis in 10 patients. Ten patients died from systemic (CAA: 8/55 (15%) and alkali: 1/67 (1.5%); p<0.05) or local (alkali: 1/67 (1.5%)) complications. More strictures (mainly oesophageal) developed in grade 3 (32%) than in grade 2 (7%) and grade 1 (8%) (p<0.05). Fifteen of 22 patients with a stricture underwent 190 endoscopic dilatations (median: 6, range: 1-84), which were successful in only 6. Nine patients needed surgery for perforation (N=5) or failure (N=4). Six stricture patients underwent direct surgical reconstruction.

In conclusion: (1) CAA ingestion has a far higher incidence of systemic complications and mortality than other caustic agents. (2) Early endoscopy is safe and gives prognostic information. (3) Endoscopic dilatation for strictures is often unsuccessful and surgery should be considered at an early stage.

TH124

OESOPHAGEAL MOTOR DYSFUNCTION IN PATIENTS WITH THE INDETERMINATE FORM OF CHAGAS' DISEASE SM Almeida, P Martins, DF Evans*, M Sanchez & DL Wingate*. GEN-CAD Service, Dept of Surgery, UFMG, Belo Horizonte, Brazil, and *GI Science Research Unit, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK.

Patients with the indeterminate form of Chagas' Disease (CD) are seropositive, without megaesophagus and asymptomatic. Small intestinal dysmotility has previously been found in CD patients without pseudo-obstruction (GE, 1995, 108: A592). Oesophageal dysmotility may also be present without dysphagia or dilatation. We used prolonged, ambulant, oesophageal manometry to test the hypothesis that motor abnormalities precede clinical manifestations of CD in the oesophagus. We studied 19 patients (12M, 7F, age 24-62) seropositive for CD; all were symptom-free. Recordings were performed for 24 hrs from a manometry catheter incorporating 3 micro strain gauges 7.5 cm apart positioned in the oesophagus and connected to a digital datalogger; patients were studied in hospital but were freely mobile. Data were downloaded for computer analysis of the incidence, amplitude and type (peristaltic, simultaneous, incomplete, and retrograde) of oesophageal contractions and compared with published data on healthy controls (GE, 1996, 110: A624).

74% patients had evidence of impaired oesophageal peristalsis (Median of abnormal v normal contractions) (33.75% v 64.6%, p<0.001) and incomplete propagation (49% v 23.5%, p<0.002), but no increase in simultaneous contractions (13.3% v 7.6%, p=0.07) or retrograde contractions which were rarely seen (0-3% both groups). Contractile amplitude, duration and propagation velocity were similar for all patients and within normal limits and there was no manometric evidence of dilatation.

The data confirm that impaired peristalsis precedes the clinical manifestations of oesophageal involvement in Chagas' disease. This is a useful model for the study of the evolution of oesophageal denervation, and of the factors that determine progression of oesophageal neuropathy that has an outcome similar to achalasia. Long term surveillance of progression of 'non-specific motility disorders' may be desirable in the light of these findings.

TH125

LOXIGLUMIDE INHIBITS POST-PRANDIAL TRANSIENT LOWER OESOPHAGEAL SPHINCTER RELAXATIONS IN PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX DISEASE

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Transient lower oesophageal sphincter relaxation (TLOSR) frequency increases and lower oesophageal sphincter (LOS) pressure falls following a fat meal. We have previously shown that these effects are attenuated in healthy volunteers by the cholecystokinin (CCK_A) antagonist loxiglumide. We have therefore studied the effects of loxiglumide on postprandial LOS function in patients with reflux disease.

Nine patients (3M, 33-66 years), with symptomatic reflux disease and excess acid exposure, were studied on two separate occasions. After a four hour fast, each patient was intubated with a manometric assembly, incorporating a Dent sleeve, and a pH probe and studied supine. Following a 60 minute basal period, patients were randomly assigned to receive intravenous loxiglumide (30mg/kg/hour for 10 minutes and then 10mg/kg/hour) or placebo. After 20 minutes, a 300ml, 200 kcal, long chain triglyceride meal (Calogen) was infused into the stomach. Manometric and pH data were recorded for a further two hours.

TLOSRS occurred more frequently in the post-prandial period during placebo (median 0 (range 0-3) to 1(0-15) (p=0.03, Wilcoxon signed rank test)), but not during loxiglumide (0 to 0(0-7)). Post-prandial TLOSR frequency was significantly reduced during loxiglumide (p=0.04 cf. placebo). Basal LOS pressure fell during the placebo postprandial period from 11(6-27)mmHg to 9(2-29), but not during loxiglumide (14(4-23) to 14(2-50)) (p=0.05 cf. placebo). Fewer reflux episodes occurred during loxiglumide infusion (1(0-8)) than during placebo infusion (2(0-19)), but this difference failed to reach statistical significance.

Loxiglumide inhibits TLOSRS and attenuates the fall in basal LOS pressure following a fat meal in patients with reflux disease. CCK may play an important role in mediating the post-prandial increase in TLOSRS and fall in basal LOS pressure, suggesting a therapeutic role for loxiglumide in the management of reflux disease.

TH127

NATURAL HISTORY OF REFLUX ESOPHAGITIS: A 5-YEAR FOLLOW UP STUDY

F. Pace, G. Manzionna, S. Bollani, G. Bianchi Porro. Gastrointestinal Unit, L. Sacco Hospital, Milan, Italy. Data concerning the natural history of reflux esophagitis (RE) are scarce and conflicting: in particular, it is not clear whether or not, in the long-term, the majority of patients still require therapy. Therefore, we investigated retrospectively the fate of our patients with RE ten years after the first endoscopic diagnosis. A number of parameters were assessed by means of a structured telephone interview, concerning the outcome of the patient, actual therapy (if any), satisfaction with treatment, and quality of life, during the last year.

Results: the records were retrieved for 288 patients where a diagnosis of reflux esophagitis had been made during the period 1983/86. Data were available for 133 patients (M/F = 93/40), followed up for a median duration of 9.8 yrs (range 4.6-15.2); 2 patients had died in the meantime (in both cases for reasons unrelated to RE), and 153 patients were no longer available. The vast majority of patients (96%) were still assuming maintenance therapy (in 61% a proton pump inhibitor [PPI], in 29% a H₂-receptor antagonist [H₂-RA], in 10% other therapies, such as prokinetics, antacids, etc). Only a minority (31%) of patients was still symptomatic during the last year of follow up. During the entire follow up period, 21% of patients had more than three endoscopic relapses, 23% between two and three, 28% one, and 28% zero, respectively. A large proportion of patients (79%) was still adopting non-pharmacological measures (diet, posture, etc.) suggested by their doctors. Only 2 patients (1.5%) had been submitted to surgery for the control of their untractable symptoms/mucosal lesions. Finally, the quality of life (QoL) appeared to have been partially improved by therapy (in particular by PPIs): 64% and 11%, respectively, considered their QoL as good or excellent, respectively.

Conclusions: contrary to many previous reports, it appears that the prognosis of RE is not favourable; the disease shows a marked trend to chronicity, leads to almost continuous drug assumption for symptom control, and is associated with a high relapse risk after treatment discontinuation.

TH126

SIMULTANEOUS AMBULATORY OESOPHAGEAL MOTILITY AND DUODENOGASTRO-OESOPHAGEAL REFLUX MEASUREMENT

Anne Smythe, Nigel Bird, Sarah Laban and Alan Johnson. University Department of Surgical and Anaesthetic Sciences, Royal Hallamshire Hospital, Sheffield.

Although ambulatory methods for duodenogastro-oesophageal reflux (DGOR) and oesophageal motility are available, simultaneous measurement has not been reported. The aim of this work was to carry out these measurements on a group of volunteers during fasting, fed, supine and upright conditions to obtain a detailed picture of oesophageal motility during DGOR episodes.

8 volunteers were studied, asymptomatic for oesophageal reflux but who in previous investigations had demonstrated periods of DGOR. Using a 3 pressure transducer assembly attached to a Gastroscan 11 data logger (MIC, Solothurn, Switzerland) the position of the gastro-oesophageal junction (GOJ) was obtained. A sodium ion selective electrode attached to a Nymph data logger (Albyn Medical, Scotland) was placed 5cm above the GOJ, alongside the distal pressure transducer, the two other pressure transducers being positioned at 10 and 15cm above the GOJ, and sodium ion measurement was carried out to assess DGOR together with wave propagation characteristics.

Sodium ion concentration could be measured during fasting, fed and ambulatory periods, and interference from meals was short lived. (Range 4-17 minutes from onset of meal). During periods of DGOR, motility patterns showed a reduction in the rate of propagated peristaltic waves compared to the preceding 5 minutes (1.5 ± 0.3 v 2.2 ± 0.3, p= 0.018). Simultaneous waves occurred in only 1 out of 17 pre-DGOR 5 minute periods but were seen in 5 out of 17 DGOR episodes, but there was no evidence of retrograde peristalsis.

Simultaneous ambulatory oesophageal motility and sodium ion measurement gives a detailed study of events during reflux of duodenal contents into the oesophagus. The diminished activity during DGOR may lead to delayed clearance and increased oesophageal damage.

TH128

DEPRESSION AND LIFE EVENTS IN PATIENTS REFERRED WITH GASTRO-OESOPHAGEAL REFLUX SYMPTOMS

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Background: Anxiety and depression are thought to be more common in patients with reflux than control subjects. We examined whether recent unpleasant life events could be contributing to excess psychological morbidity in such patients.

Methods: We studied 165 patients referred by general practitioners to our endoscopy service for investigation of reflux symptoms. Inclusion criteria were primary symptoms of heartburn, acid regurgitation and/or burning retrosternal pain. A control group comprised 79 patients having minor operations under local anaesthesia. All patients completed self-report hospital anxiety and depression (HAD) questionnaires and Brugha threatening life experience checklists.

Results: Among the reflux group 57 patients had hiatus hernia only at endoscopy. 37 had oesophagitis only, 38 patients had both, 8 had gastritis/erosions/duodenitis and 40 had normal findings. The reflux patients gave higher HAD scores than the control group (mean 27.8 vs 24.1, p<0.001). Life events during the preceding year had been no more common among the reflux group than the controls (median of one event per person in each group), and life event severity scores were no different (median 5 per person in each group). There was a weak but significant correlation between HAD and life event severity scores in the reflux group (r = 0.097, p<0.001).

Conclusions: This large study confirms that anxiety and depression scores are higher in patients with reflux symptoms than controls. Personality traits, and indeed perhaps reflux itself, probably contribute more to the excess psychological morbidity than life events.

TH129

PATHOLOGICAL GASTROESOPHAGEAL REFLUX (GER) IN PATIENTS WITH A GALLBLADDER (GB) *IN SITU* AND SMALL GALLSTONES.

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Cholecystectomy may enhance pathological GER in symptomatic gallstone patients (*Br J Surg* 1993; 80:50-3). Little is known, however, on gastro-oesophageal pH profiles in gallstone patients with a GB *in situ*, patent cystic duct and small stone burden.

Methods: ambulatory 24-h gastroesophageal pH monitoring was done in 23 patients with symptomatic gallstones (8M/15F, mean age 45 yrs [range 21-74], BMI 24.1 Kg m⁻²), an opacified GB (total cholecystogram) and a gallstone burden <20% of fasting GB volume (ultrasonography) and 21 controls (11M/10F; 44 yrs [range 25-87], BMI 24.0 Kg m⁻²). Heartburn and/or acid regurgitation were reported by 75% of patients. Data of pH were examined in the fasting period and after a standardized diet.

Results: 80% of patients had abnormal gastric and/or esophageal pH in the fasting state (GER in 69% of patients). In the fasting period, gallstone patients had higher % esophageal time at pH<4 (median[range]) 16.0[0.73]% vs 1.7[0.2-5.5]%. $P<0.005$; more GER episodes and GER episodes > 5 min ($P<0.005$) and longer GER episodes ($P<0.005$) than controls. GER episodes were symptomatic (i.e. heartburn within 2 min. of esophageal pH decrease) in 39% of patients. Postprandially, gallstone patients had significantly more GER than controls ($P<0.05$). The prevalence of gastric alkaline shift in the fasting state (i.e. proportion of time at pH>4) tended to be higher in patients than controls (35% vs 19%, P NS). Postprandial gastric pH was comparable between patients and controls.

Conclusions: The presence of symptoms evocative of GER should be investigated in gallstone patients with a *functioning* GB and small gallstones since they have significant GER which might benefit from a diagnostic/therapeutic approach.

TH131

IS H PYLORI PROTECTIVE AGAINST GASTRO-OESOPHAGEAL REFLUX DISEASE?

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H pylori colonisation of the stomach has been incriminated in a wide variety of upper GI and non-GI disorders. So far, there is little evidence to link the presence of H pylori with gastro-oesophageal reflux disease. Symptoms of gastro-oesophageal reflux (GOR) are extremely common and this study was designed to explore any association between GOR and infection with H pylori.

Method: Patients with long-standing symptoms of GOR were recruited. Symptoms of GOR were scored using the DeMeester questionnaire. All patients underwent upper GI endoscopy and the presence of H pylori was determined using antral biopsy and rapid urease test. Patients with either a normal upper GI endoscopy or oesophagitis were included in the study. Patients with additional upper GI pathology or who had received antibiotics and/or proton pump inhibitors within the previous six weeks were excluded. A control group of 196 patients matched for sex and age were tested serologically using a Helico G2 kit to determine H pylori status.

Results: 45 patients were studied (24 male, 21 female, mean age 49.6 years). The mean DeMeester reflux score was 5.1 (range 3 to 9) and symptoms of reflux had been present for a mean of 3 years (range 2 months to 20 years). 32 patients had a normal upper GI endoscopy, 13 patients had evidence of oesophagitis and/or hiatus hernia. Only 3 patients were positive for H pylori and 42 patients were negative. This gave a prevalence of 6.7% for the presence of H pylori in the study population. This was significantly ($p<0.01$) less than in the control group (37.5% positive).

Conclusions: Routine testing for H pylori in patients with symptoms of GOR is inappropriate and is likely to lead to a positive result in less than 10% of cases. This study has shown, for the first time, a very low prevalence of H pylori in patients with GOR. Could the presence of H pylori in some way protect against symptoms of GOR?

TH130

THE IMPACT OF BREAST FEEDING, ATOPY AND OTHER FACTORS ON THE PREVALENCE OF GASTRO-OESOPHAGEAL REFLUX

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Gastro-oesophageal reflux (GOR) is the involuntary passage of gastric contents into the oesophagus. It becomes pathological if its frequency and intensity is increased or if complications arise. A few studies elude to epidemiology of GOR (Carré 1959) but there are no paediatric population based studies in this field.

Aims: We have attempted to look at the prevalence of GOR in children aged 6 months and 18 months and its association with factors such as breast feeding, social background, atopy, other symptoms and hospital admissions.

Methods: The study is based on the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), a longitudinal population-based study starting in pregnancy and following all children to the age of 7 years. A series of self-completion questionnaires have been distributed to mothers and partners at various set times. For the purposes of this study GOR was defined as being present if a child "often vomited". Vomiting was defined as "bringing up most or all of the feed". The data for this study is based on questionnaires completed at 6 and 18 months.

Results: The prevalence of GOR in children aged 6 months is 4.3%. By 18 months the prevalence is reduced to 1.5%. At 6 months breast-fed infants have a lower prevalence of GOR (4.0%) compared to their non breast-fed counterparts (5.3%) ($p<0.001$). Serum IgE is not associated with GOR but wheezing and family history of atopy are. Eczema is associated with GOR at 6 months but not at 18 months. Of children with GOR at 6 months 26.3% were admitted to hospital, the figure for 18 months is 25.3%.

Conclusions: In this large prospective population based longitudinal study the prevalence of GOR is 4.3% at 6 months and 1.5% by 18 months. Breast feeding reduces the possibility of GOR. Wheezing and family history of atopy are associated with GOR. Children with symptoms of GOR have a high risk (1 in 4) of being admitted to hospital.

TH132

FORCES EXERTED DURING OESOPHAGEAL DILATATION

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Aim: An electronic device was designed and built for use during oesophageal dilatation to allow measurement of the forces exerted on a bougie dilator during dilatation. **Methods:** The device featured a handle designed in the shape of hinged split cylinder which could be locked around the dilator but could be readily moved up and down the shaft as the dilatation proceeded if necessary. The handle consisted of two parts, one that gripped the dilator and the other that was gripped by the clinician. One of the members that joined these parts together contained strain gauges arranged as a Wheatstone bridge so that the forces transmitted by the clinician's hand could be measured accurately. The device was designed to measure and also record the push and pull forces exerted during the examination. The force measurements were recorded using a computer which stored the data on disk while in real time it displayed the data graphically as a chart recorder style trace on the screen. The device was calibrated against a range of weights exerting force on a bougie dilator using a pulley system and was shown to give reproducible linear measurements of force over the range of interest. A series of interchangeable split cylinders allowed it to be used with different sizes of dilator. The device was electronically isolated from the patient. **Results:** This device was used to measure the forces at dilatation in 10 patients using 2 thermoelastic oesophageal dilators of 13 and 18 mm diameter (Savary, Celestin). Peak forces varied from 0.4 to 3.8 Kg force for the large 18 mm dilator and 1 to 2.2 Kg for the small 13 mm dilator. The mean peak force for the 18 mm dilator was 2.3 Kg and the mean peak force for the 13 mm dilator was 1.5 Kg. The force exerted in order to pass the cricopharyngeus was 0.25 - 1.3 Kg. The length of time that forward thrust was transmitted to the patient's oesophagus was 10-21 sec. Peak retrograde force on removing the dilator was -0.4 Kg. In all these cases the clinician felt he was applying only low or moderate force. **Conclusion:** These measurements represent the first accurate measurements of the forces exerted during oesophageal bougienage.

TH133

Gastroesophageal reflux as a complication of achalasia therapy.**M Dakkak, JGC Cox, JR Bennett, Hull Royal Infirmary, Hull.**

Gastroesophageal reflux is a recognised complication of achalasia therapy, whether by cardiomyotomy or by balloon dilatation. Reflux is often disregarded by the patient or the doctor unless it is very troublesome.

Our series consists of 176 patients, 38 cases were treated surgically while 138 were treated with balloon dilatation. The patients were followed up carefully in one centre over 27 years.

There were 47 cases of reflux. 27 of these cases were recognised by symptoms, by endoscopy or by 24 h pH monitoring and were satisfactorily treated with medical therapy.

There were 20 other cases in which peptic strictures developed and required stricture dilatation. There were 10 cases of strictures among the patients who were treated by balloon dilatation and a similar number of patients developed stricture among the patients who had cardiomyotomy. The mean period between achalasia therapy and the diagnosis of stricture was 6.0 ± 5.14 years in the dilatation group and 16.2 ± 9.07 years in the surgical group.

The diameter of the balloon used did not appear to influence the likelihood of subsequent reflux or stricture. None of the patients in the surgical group who had an anti-reflux procedure performed at the time of cardiomyotomy developed a peptic stricture.

Conclusions:

1. A high proportion of patients treated for achalasia develop reflux complications.
2. Anti-reflux procedure at the time of cardiomyotomy may prevent the development of a peptic stricture.

TH135

ENDOSCOPIC GASTROPLASTY FOR GASTRO-OESOPHAGEAL REFLUX DISEASE. C.P. Swain, SS Kadairkamanathan, F Gong, D Evans. Royal London Hospital, Whitechapel, London E1 1BB, UK

Aim: The aim of this study was to perform and record the results of endoscopic gastroplasty in a series of patients. **Methods:** Endoscopic Gastroplasty was performed at flexible endoscopy in 28 patients with gastro-oesophageal reflux disease uncontrolled by long-term medical therapy and who were offered and declined anti-reflux surgery (open or laparoscopic) or were deemed unfit for general anaesthesia due to concurrent illness. GORD was confirmed by pre-operative manometry and 24 hour ambulatory pH studies. Using a 9mm diameter endoscopic sewing machine a neo-oesophagus of 1-2 cm was created below the cardio-oesophageal junction by placing nylon sutures and securing the tissue with 4 half-hitches tied extracorporeally. **Results:** The operation was performed as a day-case procedure under sedation (usually diazepam 20 mg and pethidine 50 mg IV) and the median duration of the procedure was 35 minutes. Post-operative assessment was made at a median of 12 weeks (8-52) with respect to symptoms, manometry and 24 hour ambulatory pH studies. Symptoms assessed by DeMeester symptom score improved from a median of 5 to 1 [$p < 0.05$]. Median lower oesophageal sphincter length increased from 1.9 to 2.9 cm [$p < 0.05$] and pressure increased from 5.25 to 8.25 mm Hg [$p < 0.05$]. The median (range) % time pH < 4 decreased from 8.4 (0.5-16.4) to 2.7 (0-8.1) [$p < 0.05$]. Complications included minor haematemesis in one patient, transient dysphagia in 3, in one patient with thoracogastric adhesions following thoracoplasty the endoscopic stitches cut out and a surgical Nissen fundoplication was performed. Repeat pH measurements at 1 year post procedure in 2 patients showed no reflux. **Conclusion:** In this series, endoscopic gastroplasty significantly improved symptoms reduced acid reflux, and increased sphincter length and pressure. Potential advantages of this procedures include easy repeatability, reversibility, short operation time, lack of need for general anaesthesia. Endoscopic gastroplasty has a short term efficacy comparable to operative fundoplication, but with a much lower utilization of health care resources.

TH134

Ten-year follow up after forceful balloon dilatation of achalasia. M Dakkak, JR Bennett. Hull Royal Infirmary, Hull.

Achalasia is a condition which occurs infrequently resulting in relatively small numbers in many series and the tendency to provide data on short or medium term follow up. 66 new cases of achalasia were diagnosed and treated with forceful balloon dilatation in one centre between 1971 and 1986. Contrast radiological examinations were performed following each dilatation. Careful clinical and radiological follow up for more than 10 years has been carried out (699 patient-year).

Contrast radiological studies revealed 3 cases of perforation. 2 were treated conservatively and recovered well, while one patient was treated surgically and subsequently died.

The long term outcome has been satisfactory in the majority, with 45 (68%) having an excellent result, 13 (20%) with a modest result and 8 (12%) whose results were less satisfactory.

In most cases one dilatation was sufficient, but 18 (27%) required further balloon dilatation.

Long term follow up revealed 18 patients (27%) with symptomatic gastroesophageal reflux, 8 (12%) of these developed peptic strictures. Only 3 of these patients with reflux had more than one balloon dilatation.

12 patients died during the follow up from unrelated causes.

Conclusion:

Forceful balloon dilatation remains a simple, safe and satisfactory form of treatment for achalasia, but long term follow up reveals that a third of the patients suffer from subsequent reflux.

TH136

WITHDRAWN

TH137

LONG TERM OBJECTIVE FOLLOW UP AFTER LAPAROSCOPIC FUNDOPPLICATION IN PATIENTS WITH REFRACTORY GASTRO-OESOPHAGEAL REFLUX DISEASE. L.Rogers, S.S.Kadirkamanathan, D.F.Evans, S.M.Scott. Academic Surgical Unit and Gastrointestinal Science Unit, The Royal London Hospital Medical College, London, UK

Laparoscopic fundoplication (LF) was performed on 166 consecutive patients (male 100, female 66) with gastro-oesophageal reflux disease (GORD) who were refractory to medical treatment. Diagnosis of GORD was confirmed by 24 hour ambulatory pH studies. Ninety six patients continued to take proton pump inhibitors and these underwent an additional pH study on therapy. Median age of patient group was 42 years (range 16-82) and median symptom duration was 48 months (3-600). LF was performed using 3 to 4 sutures to create a 2 to 3 cm floppy wrap. There were no conversions. Median operating time was 68 minutes (33-330) and the median hospital stay was 2 days (0-5). Post-operative assessment was made at a median of 47 days (26-76) with respect to symptoms, lower oesophageal sphincter (LOS) function on manometry and 24 hour ambulatory pH studies. To date 52 patients have been followed up for over 12 months, 14 over 24 months and two up to 36 months. Symptoms assessed independently using DeMeester symptom score improved significantly from a pre-treatment median score of 5 (2-8) to 4 (2-9) [$p=0.02$] while on anti reflux medication but, LF markedly reduced the symptom score to 1 (0-6) which was significantly better than both ON and OFF treatment [$p<0.0001$ & 0.0001]. The symptom improvement was maintained at 1,2 and 3 year follow up (median symptom score 1). Acid exposure of distal oesophagus ON medication was no different to that OFF medication. [% time pH < 4 ON was 4.8 (0.5-58.8) and OFF was 7.6 (1.3-25.1) $p=0.06$]. LF produced effective control of acid reflux which was significantly better than both ON and OFF medication: [% time pH < 4; 0.4 (0-11.5) [$p<0.0001$ & $p<0.0001$]]. The median % time < 4 was 0.6 at one year, 0.3 at two years after LF confirming that effective control of acid reflux was maintained. LF also produced significant increases in median LOS pressure from 6 (0-25) to 13.5 (5.5-27.75) mmHg [$p<0.0001$] and length from 2 (1-4) to 3.5 (2-5) cm [$p<0.0001$]. These data shows that LF is effective in controlling the symptoms and distal oesophageal acid exposure in patients with refractory GORD for at least 36 months.

TH138

ANOTHER VIEW ON LAPAROSCOPIC ANTI- REFLUX SURGERY
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Aims: Measurement of outcome for laparoscopic antireflux surgery (LARS) has to date been confined to the technical feasibility, its impact on symptomatology and the financial implication of its introduction. As no data are available from the patients' perspective about the quality of life (QoL) following its introduction, this study was designed to obtain preliminary information in such patients.

Methods: All patients selected for LARS were requested to complete QOL questionnaires (SF36, Euroqual) both prior to and 6 months following surgery. Twenty-six patients have been studied. All patients had manometric evidence of gross incompetence at the lower oesophageal sphincter, with deranged pH profiles (mean De Meester score 58 ± 18 SEM).

Results are shown in table

SF 36 profile	Pre LARS Med (I.Q. range)	Post LARS Med (I.Q. range)	Wilcoxon
Physical function	62 (35 - 84)	75 (55 - 95)	0.44
Functional Role	50 (16 - 78)	88 (48 - 91)	0.006**
Pain Score	30 (20 - 60)	72 (61 - 82)	0.015*
General Health	47 (25 - 65)	74 (49 - 87)	0.096
Vitality	50 (20 - 66)	60 (35 - 70)	0.58
Social Function	62 (37 - 87)	87 (62 - 95)	0.14
Emotional role	64 (46 - 100)	77 (33 - 100)	0.1
Mental Health	60 (48 - 78)	64 (52 - 84)	0.84
Life Quality (QoL)	25 (0 - 61)	61 (25 - 84)	0.02*
Euroqual	40 (25 - 58)	80 (60 - 90)	0.015*

** $p < 0.01$, * $p < 0.05$

Conclusion: No change in the psychological or social domains was noted following surgery, although significant improvements were noted in the physical role, pain scores and overall health-related QoL. Further evaluation of both surgical and medical therapies of gastro-oesophageal reflux is needed to establish the long term benefits as perceived by the patient, rather than by the clinician in order to compare the value of these two treatments.

TH139

THOROSCOPIC ASSISTED TRANSHIATAL OESOPHAGECTOMY- NEW LAMPS FOR OLD?

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Surgical excision remains the best chance of long term survival for patients with oesophageal carcinoma. The advent of minimal access surgery allows accurate dissection and thoroscopic mobilisation of the oesophagus without the need for thoracotomy and its associated complications. We report our experience of thoroscopic-assisted transhiatal oesophagectomy (TATH) between December 1993 and June 1996. Forty-two consecutive patients underwent TATH. Twelve patients required conversion to thoracotomy because of pulmonary adhesions, size of tumour, tracheal injuries or ventilation difficulties. The mean age of the patients was 65.7 (45-80) years. The stricture length was between 3-11cm in the TATH and 5-12cm in the conversion group. average total operation time was 308 minutes (235-400) in the TATH, thoroscopic dissection taking 83 minutes (50-120). One death occurred in each group. The mean post operative hospital stay was 14 days in both groups. The 1 and 2 year survival rates were 71% (30 of 42) and 60% (25 of 42) respectively. The results of TATH are very similar to those of conventional surgery. We propose that TATH may offer an advantage in terms of visualisation of mediastinal structures during dissection, thus minimising operative complications.

TH140

THE UK NATIONAL BARRETT'S OESOPHAGUS REGISTRY

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A UK National Registry of Barrett's Oesophagus (BO) patients was established in June 1996 as a joint initiative between the Oesophageal Section of the BSG and the European Cancer Prevention Organisation (ECP). Since then over 500 patients have been registered from the first 3 centres and this communication reports the results of a pilot study of data from two of these centres in adjoining health districts. The hospitals were Wexham Park Hospital, Slough (WPH), catchment population 360,000, and Wycombe General Hospital, High Wycombe (WGH), catchment population 220,000. At WPH the visual diagnosis of BO was initially made at endoscopy irrespective of length of involved segment and confirmed histologically in at least 76%. At WGH the diagnosis was only considered in segments of approximately 4cm or more, but all of these had histological confirmation of BO.

Between January 1991 and August 1996, 424 BO cases were registered at WPH. There was a male preponderance of 1.5:1, the mean age being 65 years for males and 70 years for females. In the period July 1995 to June 1996 197 BO patients were endoscoped at WPH (M:F 1.7, mean ages 62 and 71 years respectively) and 71 BO patients at WGH (M:F 1.7, mean ages 62 and 69 years respectively).

Adenocarcinoma of the oesophagus was diagnosed at WPH in 5/424 (1 in 85) patients between January 1991 - June 1996, of whom 2 were diagnosed in the period July 1995 - June 1996 and in 1 patient (1 in 71) at WGH in the latter period.

These data confirm the practicality of running a multicentre BO Registry, establishing comparisons of diagnostic criteria of BO in different departments and variations with time. The Registry is now being extended first to the Anglia/Oxford Region and then to the whole of the United Kingdom.

TH141

INCREASING INCIDENCE OF BARRETT'S OESOPHAGUS: DIAGNOSTIC ZEAL OR GENUINE OBSERVATION?

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Barrett's oesophagus is the major recognised risk factor for the development of oesophageal adenocarcinoma. It is well documented that the incidence of oesophageal adenocarcinoma is rising, and one might suspect that this is paralleled by an increase in the incidence of Barrett's oesophagus. We have studied the incidence of Barrett's oesophagus in Tayside to determine whether there is an increasing incidence in the diagnosis of Barrett's oesophagus.

The incidence of endoscopically diagnosed Barrett's oesophagus was determined by searching the endoscopy database for years 1980-1993. This represented 53,433 endoscopies performed in our population of 384,000. 961 new cases of endoscopically diagnosed Barrett's oesophagus were identified representing 18 new cases/100,000/year (18 cases/1,000 endoscopies). The incidence was not constant throughout, but showed a dramatic rise from 1/100,000/year (1.4/1,000 endoscopies) in 1980/81 to 48/100,000/year (42.7/1,000 endoscopies) in 1992/93. When only cases with histological confirmation were considered, the incidence for 1992/93 was 18/100,000/year (16.5/1,000 endoscopies).

We have demonstrated a significant rise in the incidence of Barrett's oesophagus. This may be partially explained by an initial low incidence, possibly due to a failure to recognise Barrett's oesophagus endoscopically, combined with a change in endoscopic referral patterns (possibly more reflux disease) and/or an overzealous attitude to the endoscopic diagnosis of Barrett's oesophagus. However, we believe there is a true increase in the incidence of Barrett's oesophagus in our population. The cause of this increasing incidence is unknown, but it may be related to the increasing incidence of oesophageal adenocarcinoma.

TH143

PREVALENCE OF SPECIALISED COLUMNAR EPITHELIUM AT THE CARDIA OF PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX WITHOUT OBVIOUS BARRETT'S OESOPHAGUS; COMPARISON WITH NORMAL CONTROLS. B.T.Cooper, M.A.Cox, J.C.Gearty, Gastroenterology Unit, City Hospital, Dudley Road, Birmingham, B18 7QH, UK.

Previously unsuspected specialised columnar epithelium (SCE) has been reported in biopsies of the cardia from 18% of unselected patients undergoing endoscopy (1). This may be relevant in the increasing prevalence of adenocarcinoma in the distal oesophagus and at the cardia and raises the question whether Barrett's oesophagus is much commoner than previously thought. In this study, we have looked at the prevalence of SCE at the cardia of 54 consecutive patients with symptoms of gastro-oesophageal reflux (GOR). 15 of the 54 had mild erosive reflux oesophagitis (Savary Miller grades 1&2) and 13 of the 54 had erythema of the distal oesophagus without erosions. The results were compared with 18 normal controls who had neither symptoms of GOR nor any endoscopic abnormality of the upper GI tract. Patients with more severe endoscopic GORD including Barrett's oesophagus were excluded. The 54 GOR patients (33 females) were aged 23-83 mean 56 years and the 18 controls (11 females) were aged 22-75 mean 45 years. At least 3 large endoscopic biopsies were taken from below the squamo-columnar junction at the cardia in each patient, stained with haematoxylin/eosin and alcian blue/PAS diastase and assessed histologically for the presence of SCE by one pathologist (JCG) who was unaware of the clinical or endoscopic features. 29 (53.7%) of the patients with GOR had SCE at the cardia compared to 4 (22.2%) of the controls ($\chi^2=5.38$; $P<0.02$). There was no correlation between SCE at the cardia and age, sex and the presence of reflux oesophagitis at endoscopy. We conclude that SCE is relatively common in both groups but is commoner in patients with GOR than controls. However it must be doubtful whether SCE at the cardia has the same significance as Barrett's oesophagus.

1. Spechler et al. Lancet 1994; 344:1533-6.

TH142

ACID AND BILE REFLUX IN SHORT SEGMENT BARRETT'S OESOPHAGUS.

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Barrett's oesophagus (BO) is a consequence of oesophageal exposure to severe acid and bile reflux. It has been suggested that Short Segment Barrett's oesophagus (SSBO) represents an early, metaplastic phase in the transition from normal to BO. If this is the case, oesophageal acid and bile exposure in SSBO should be greater than normal. To examine this hypothesis the aim of this study is to compare oesophageal acid and bile exposure in normal, SSBO and BO patients. **Methods:** BO is defined as ≥ 3 cm columnarisation of the distal tubular esophagus n=21; SSBO is defined as intestinal metaplasia at an otherwise normal squamocolumnar junction, n=19; and normal is defined as no BO or SSBO, n=43. Normal and SSBO patients were all symptomatic patients attending for diagnostic endoscopy. Ambulatory 24 hour oesophageal pH and bile studies were performed using a Synectics mark III Digtrapper and Bilitec 2000 system, 10 days after stopping acid suppression therapy. When possible both studies were performed simultaneously and the probes were positioned 5cms above the lower oesophageal sphincter. A positive pH study is defined as a DeMeester score >15 and a positive bile study is defined as a bilirubin exposure $>5\%$ of the supine period.

Results:	Barrett's	SSBO	Normals
No. of +ve pH studies	18/21*	11/19	24/43
Median DeMeester score	57.2**	17.9	25.6
No. of +ve bile studies	11/16	2/10	9/18
Median bilirubin exposure	9.45%	0.1%	4.9%

* $p < 0.03$ by χ^2 test. ** $p < 0.01$ by Mann-Whitney U test

Conclusion: Oesophageal acid and bile exposure in SSBO does not differ from normal but is significantly less than in BO. These results do not support the hypothesis that SSBO is an early step in the progression to BO. It is suggested that gastroesophageal reflux is not an aetiological factor for SSBO.

TH144

PATTERN OF EARLY CHROMOSOMAL ALTERATIONS IN BARRETT'S OESOPHAGUS.

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Barrett's oesophagus is the major risk factor for oesophageal adenocarcinoma. The progression to malignancy involves several genetic events, but little is known about early changes occurring in the metaplastic epithelium before dysplasia develops. **Aim:** to identify chromosomal alterations, consistent with malignant potential in non-dysplastic Barrett's mucosa. **Method:** Multiple endoscopic biopsies were taken from 17 patients with uncomplicated Barrett's oesophagus, including normal oesophagus and stomach as controls. The frozen biopsies were sectioned, clustered on slides and subjected to interphase cytogenetics. Fluorescent In-Situ Hybridisation (FISH) was performed with probes specific to chromosomes 1,8,9,12,17 & 18. Signals per nucleus were counted on 200 cells per biopsy, using fluorescent microscopy. The chromosome index(CI) was calculated (No. of signals /No. of nuclei). The mean CI for controls(n=77) was 1.58 ± 0.1 and a value >3 standard deviations from the mean was regarded as abnormal.

Results:

Chromosome	No. biopsies	No. patients	Chromosomal Changes
1	24	8	No abnormality
8	9	4	1 gain (Patient 2)
9	31	9	2 gains (Patients 2 & 5)
12	15	6	1 loss (Patient 3)
17	16	5	No abnormality
18	33	13	No abnormality
Total	128	17	4 alterations

Conclusion: Chromosomal changes occur in uncomplicated Barrett's oesophagus, at a low frequency, consistent with the hypothesis that genetic alterations are rare in non-dysplastic disease. Clonal divergence, reflecting the histological heterogeneity of Barrett's mucosa, is suggested, as changes do not occur at all biopsy sites in each patient.

TH145

AMPLIFICATION AND OVEREXPRESSION OF CYCLIN D1 IN OESOPHAGEAL CARCINOMA

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The cyclin D1 gene encodes a protein which controls the passage of the cell through the G1/S checkpoint in the cell cycle. Cyclin D1 is a proto-oncogene, since its aberrant expression could contribute to uncontrolled cell proliferation. This study investigated amplification and overexpression of cyclin D1 in oesophageal carcinoma.

Twenty-six oesophageal adenocarcinomas and 19 squamous cell carcinomas were studied. Paired tumour and normal DNA samples were analysed by Southern blotting with specific DNA probes for cyclin D1 and for a control gene (α -lactalbumin) which is present in a single copy. The cyclin D1 gene copy number was calculated for each tumour. Expression of the cyclin D1 gene was assessed by immunohistochemical analysis of its protein product, which is usually undetectable by this method in normal tissues.

Cyclin D1 gene amplification (by a factor of between 2 and 6) was identified in 7 tumours (16%); 5 were squamous cell carcinomas, 2 were adenocarcinomas. No significant association was identified between amplification and tumour T stage, N stage, or patient survival.

Overexpression of cyclin D1 protein was identified in 8 tumours (6 squamous cell carcinomas and 2 adenocarcinomas) and was significantly associated with gene amplification ($p=0.04$, Fisher's Exact test). Overexpression was also significantly associated with early T stage (T1 or T2; $p=0.01$, Fisher's Exact test). No significant association was identified between overexpression and N stage or patient survival.

There was a trend (non-significant) towards a predominance of both amplification and overexpression of cyclin D1 in squamous cell carcinomas over adenocarcinomas.

These results indicate that cyclin D1 amplification and overexpression occur commonly in oesophageal carcinoma, particularly squamous cell carcinoma. Cyclin D1 overexpression may influence tumour behaviour, causing the disease to present at an earlier T stage. The mechanism for this effect is unclear, and warrants further investigation.

TH146

ADENOCARCINOMA OF THE LOWER OESOPHAGUS AND CARDIA ARE SIMILAR BOTH EPIDEMIOLOGICALLY AND CLINICALLY: A POPULATION BASED STUDY FROM 1974 TO 1993.

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There were 5,322 cases of primary oesophageal carcinoma and 10,573 cases of primary gastric carcinoma reported to the Merseyside and Cheshire Cancer Registry (population 2.5 million) between 1974 and 1993. The ratio of oesophageal to gastric carcinoma was 1:2. Calculation of the cumulative incidence rates revealed a significant increase in oesophageal carcinoma in males over the study period. This was found to be entirely due to a rapid rise in adenocarcinoma of the oesophagus, the incidence of which trebled in males and doubled in females. Eighty-six percent of these adenocarcinomas occurred in the lower oesophagus.

The incidence of gastric carcinoma decreased in both sexes between 1974 and 1993. However, analysis of the subsite-specific incidence rates indicated that carcinoma of the cardia more than doubled in males, and almost doubled in females, whereas carcinoma at all other sites of the stomach decreased. Twenty percent of all gastric carcinoma occurred in the cardia.

The similar trends in incidence of adenocarcinoma of the oesophagus and of the cardia prompted a comparison of the epidemiological and clinical parameters of adenocarcinoma occurring in the middle oesophagus, lower oesophagus, cardia and subcardia. Adenocarcinoma of the lower oesophagus and cardia were very similar in their changing incidence, age at diagnosis, male:female ratio, percentage of patients who smoked and in their survival. Both carcinoma of the lower oesophagus and the cardia differed significantly from tumours of the subcardia. This suggests that adenocarcinoma of the lower oesophagus and gastric cardia may be the same disease, and this has important consequences for the surgical treatment of carcinoma of the cardia.

TH147

RISING INCIDENCE OF OESOPHAGEAL ADENOCARCINOMA: A 20 YEAR RETROSPECTIVE REVIEW FROM A SINGLE UNIT
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It is now recognised that the pattern of oesophageal cancer has changed dramatically. A previous report from our unit in 1991 revealed that during 1976-1990 49% of all oesophageal cancers were adenocarcinomas (AC). The review of endoscopy records has now been extended to include the next 5 year cohort, 1991-1995 inclusive. A total of 37,992 consecutive endoscopy records for the period 1976-1995 were studied retrospectively for mention of oesophageal cancer, 289 cases were identified. They were subdivided by histological type, oesophageal location, sex, age and into four cohorts of five years by year of presentation to the unit. The oesophagus was divided into two segments, above and below 32cm, by adapting the criteria suggested by the US National Cancer Institute (1989).

The mean age at diagnosis of both male and female patients with squamous cell carcinoma (SCC) had increased during the 20 years study period; in males from 67.4 years in the first, to 74.2 years in the last quartile and in females from 66.4 to 72.8 years during the same period. In contrast, whereas the age of males with AC had remained virtually unchanged (66.7 to 68.3) in females with AC the age had dropped from 74.2 to 69.9 years between the first and last quartiles. AC were located predominantly in the lower oesophagus, 132 (83%) below 32cm and 28 (17%) above 32cm. SCC were more evenly distributed; 48 (43%) below and 62 (57%) above 32cm. In line with other published series the numbers of AC had risen from 21 (45%) in the first quartile to 63 (70%) in the fourth quartile. Overall the male:female sex ratio for AC was 3:1 (M120:F40 cases) and 0.7:1 for SCC (M46:F64).

AC now represents the majority of all oesophageal cancers diagnosed in our unit, especially in males. These findings confirm a continuing rise in incidence of oesophageal AC to 70%, the highest incidence reported to date.

Eur J Cancer Prev 1991; 1: 23-25; Cancer 1989; 64: 526-30

TH148

PET SCANNING FOR ASSESSING RESECTABILITY OF OESOPHAGEAL CANCER - Preliminary results

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Aim: To determine whether PET scanning improves the accuracy of pre-operative staging with spiral CT scanning of patients with primary oesophageal carcinoma.

METHODS: 14 consecutive patients with oesophageal (10 adenocarcinoma, 4 squamous) were studied. 3 were excluded due to distant metastases detected by PET and CT scans. 11 patients with operable disease were scanned pre-operatively by spiral CT and PET scan, using the positron emitter 18F fluoro-2-deoxy-D-glucose. The findings of spiral CT and PET were assessed independently of the findings at operation and pathological examination of the resected specimen.

RESULTS: The primary tumour was visualised in 10 cases by spiral CT and in all 11 cases by PET. CT gave anatomic information of the extent of local spread which would not be expected from PET scans. Positive left gastric/coeliac lymph nodes were found in 7 cases. These were detected in 4 cases on CT (with 1 false positive) and in only 1 case by PET because of the lack of anatomical detail required to separate them from the primary. Positive mediastinal nodes were found in 5 cases. These were detected in 3 cases by CT and in 2 of these by PET. One patient had 4 x 0.5cm subcapsular liver metastases. These were detected by PET but not by CT.

CONCLUSIONS: The ability of PET scans to detect disease distant to the operative field suggests its main role may be in patients with large tumours and borderline operability. In addition PET may have a role in predicting response to neo adjuvant chemotherapy.

TH149

DOES PRIOR RADIO- AND/OR CHEMOTHERAPY PREDISPOSE TO COMPLICATIONS AFTER INTUBATION FOR MALIGNANT OESOPHAGO-GASTRIC OBSTRUCTION
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Endoscopic intubation is an effective procedure for palliation of dysphagia in patients with malignant oesophago-gastric obstruction. Prior radio- and/or chemotherapy may entail an increased risk of complications following intubation with a rigid prosthesis.

The aim of the study was: (1) to assess efficacy, complications, recurrent dysphagia and survival after intubation for palliation of dysphagia, and (2) to evaluate the relationship between prior radio- and/or chemotherapy and the occurrence of complications.

From 1988 to 1995, a consecutive series of 307 patients underwent intubation with a Celestin prosthesis under general anaesthesia for palliation of dysphagia, caused by a malignant stricture of oesophagus and cardia. Of these 307 patients, 111 (36.2%) patients had undergone prior radio- and/or chemotherapy. In 306 (99.7%) patients, a rigid prosthesis was successfully placed. The dysphagia score improved from 2.7 ± 0.6 (grading from 0 to 4) at baseline to 0.6 ± 0.8 at 4 weeks after intubation. Major complications were registered in 97 (31.7%) patients and included: perforation (22), fistula (5), haemorrhage (9), severe pain (10), aspiration (8), erosion/ulcer at the end of prosthesis (7), fever (4), migration (22), malposition (7), and fracture of prosthesis (3). Sixty-nine (22.6%) patients had recurrent dysphagia. Median survival was 67 days and hospital stay after placement was 6.6 ± 5.5 days. Prior radio- and/or chemotherapy increased the risk of perforation, fistula, haemorrhage and severe pain following intubation (26/111 vs 20/195; $p=0.0026$). Median survival was not different between patients with or without prior radio- and/or chemotherapy.

In conclusion: 1. Celestin prostheses are an effective palliative treatment for malignant dysphagia, however they carry a relatively high risk of complications and recurrent dysphagia. 2. Prior radio- and/or chemotherapy predisposes to prosthesis-related complications.

Endoscopy TH151-TH163

TH151

PATIENTS' OWN PERCEPTIONS OF ENDOSCOPY UNDER THROAT SPRAY. M Welsh, GD Smith, S Ghosh, KR Palmer.
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Background: Diagnostic endoscopy is commonly carried out in UK under IV sedation, but B.S.G guidelines suggest that this practice is not always required. Unsedated endoscopy offers advantages of quick turnover and few sedation related complications, but patients own perceptions of such a practice has not been widely studied. A nurse led study performed immediately after completion of endoscopy was used to assess patients' perceptions holistically.

Aim: To determine the acceptability of diagnostic endoscopy to patients performed under local anaesthetic spray.

Method: 76 patients who chose to undergo endoscopy after throat spray (M=36, F=40, median age 42, age range 18-70 years) were studied using a nurse administered questionnaire, explained to them prior to the procedure. The endoscopy itself was explained in detail by a nurse. Completed questionnaires were collected prior to discharge on the same day. The response rate was 100%.

Results: 71 patients (95%) considered that they had received sufficient information about the procedure. 69 patients (91%) felt that it matched their expectations. 58 patients (78%) were prepared to undergo a repeat procedure if necessary under throat spray. Abdominal pain and bloating were relatively uncommon following endoscopy (8% and 17% respectively), but, despite anaesthetic throat spray (Xylocaine spray, Astra) 38 patients (50%) complained of a sore throat within 30 minutes of the procedure. 19 (25%) patients received regular oral suction during the procedure to avoid the uncomfortable feeling of drowning in their own saliva, and described it as helpful.

Conclusion: Endoscopy under throat spray was well accepted in a selected group of patients who chose to have the procedure done unsedated. Patients generally felt well post-procedure but sore throat was a common problem despite local anaesthetic spray. The effectiveness and dose of throat spray may need further study. Pre-procedure detailed explanation helps to alleviate anxiety and match the expectations with the actual procedure.

TH150

QUALITY OF LIFE FOLLOWING STENT INSERTION IN MALIGNANT OESOPHAGEAL STENOSIS: A RANDOMISED TRIAL COMPARING METAL AND PLASTIC STENTS.

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Background: Metal stents are widely used in palliation of oesophageal carcinoma but their advantage over plastic tubes has yet to be proven.

Aim: To compare the effect of Gianturco metal stents with Atkinson tubes on quality of life in malignant oesophageal obstruction.

Methods: Thirty one consecutive patients with inoperable malignant oesophageal obstruction were randomised, patient single blind, to receive either a modified Gianturco silicone-covered metal Z stent (n=15) or a plastic Atkinson tube (n=16). Sedation was similar in each group and patients were given identical dietary advice. Data were collected by a specialist nurse before insertion, one week after and thereafter 6 weekly until the patient's death. Quality of life at each time point was assessed using the Nottingham Health Profile (NHP).

Results: Three stent-related deaths occurred in the first week following insertion of an Atkinson tube with only one in the Gianturco group. Complication rates were otherwise similar in the two groups. The table shows outcome variables between the groups after insertion.

	wks	Gianturco	Atkinson	p
% change in weight (from original wt)	1	-0.6(-2.9+0.8)*	-4.5(-7.1--0.5) *	0.05
	7	0.8(-3.1+1.9)*	-7.3(-11.1+2.5)	0.13
% of patients with no dysphagia	1	50%	38%	0.55
	7	89%	50%	0.09
% of patients with improved appetite	1	57%	23%	0.07
	7	89%	33%	0.02

* Median (inter-quartile range)

Patients in the Gianturco group showed greater improvements in NHP parameters following insertion of the stent than those in the Atkinson group. (Energy: $p=0.04$; emotion: $p=0.06$; social isolation: $p=0.05$).

Conclusion: Patients treated with Gianturco stents maintain their weight for longer, with improved swallowing, appetite and quality of life when compared to those with Atkinson tubes.

TH152

THE COLORECTAL NURSE ENDOSCOPIST - INITIAL RESULTS Moshakis V., Ruban R.C.
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Introduction - Over a one year period a Nurse Endoscopist was trained in flexible sigmoidoscopy and clinical coloproctology. Following assessment the Nurse Endoscopist was able to practice sigmoidoscopy as part of the colorectal endoscopy service.

Method - Sigmoidoscopy was performed in patients referred directly to the one-stop clinic, from the outpatients department and general surgical wards. Comprehensive Practice Protocols were followed. Informed consent was obtained. A video recording of every procedure was taken. A "Sigmoidoscopy Report" was issued to the referring doctor on completion of each procedure.

Sigmoidoscopy results were then audited.

Results - 400 procedures were performed over an 8 month period. 81% of patients were referred to the one-stop clinic. 50-60 cm insertion depth was achieved in 70% of patients. The descending colon/splenic flexure was reached in 70.5% of cases. Principle clinical findings were: - carcinoma (4.75%); polyp (17%); inflammatory bowel disease (12.75%); haemorrhoids (31.75%); diverticuli (7.25%) and normal findings (23%). (*Some patients had > 1 diagnosis/finding). Biopsy and injection sclerotherapy was indicated in 38% and 35.75% of cases respectively. Follow-up included outpatients clinic (40.25%); discharge (38%) and colonoscopy/barium enema (17%). There was no morbidity or mortality.

Discussion - Audit shows that, following a period of intensive training and assessment, a Nurse Endoscopist is able to perform independent flexible sigmoidoscopy competently and safely.

TH153

COMMUNITY BASED OPEN ACCESS NURSE LED FLEXIBLE SIGMOIDOSCOPY FOR RECTAL BLEEDING

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A direct access nurse led endoscopy service based at 6 community sites was launched following a 6 month nurse training period. Patients with rectal bleeding are referred directly to the nurse by general practitioners and an appointment sent by return of post. Clinics are staffed by a nurse endoscopist and nursing auxiliary.

79 patients were endoscoped by the nurse endoscopist (48 female, median age 63 years [range 23 - 89]). 67 patients complained of rectal bleeding (81% bright red blood, 19% dark, 48% mixed in with motions). Other symptoms included abdominal pain (30%), change in bowel habit (38%) and weight loss (13%).

One patient had two cancers at endoscopy, 8% had polyps, 8% diverticular disease and 20% had significant haemorrhoids. 60% were normal. Median depth of endoscopy 55 cm (range 10-60cm).

Patient satisfaction was recorded using a postal questionnaire. 96% felt the examination was worthwhile, the staff helpful and that a full explanation of the procedure had been given. 27% found the examination embarrassing and 53% painful, of these 8% required analgesia and 21% sought medical advice. 94% would be prepared to undergo the examination again.

In conclusion, a nurse led open access flexible sigmoidoscopy service is feasible, acceptable to patients and yields pathology in up to 40% of patients.

TH154

APHTHOUS ULCERATION IN THE TERMINAL ILEUM : WHAT IS THE SIGNIFICANCE ? D.Suri, B.P. Saunders, J.D. Sanderson. Dept. of Gastroenterology, Guy's and St. Thomas' Hospitals, London SE1 9RT.

Aphthous ulceration is a well-recognised feature of number of inflammatory bowel diseases but a particular hallmark of Crohn's disease (CD). At ileocolonoscopy, the finding of ileal aphthous ulcers is not infrequent. In a previous study, ileal aphthae were demonstrated as the sole finding in 11% of patients of patients undergoing ileocolonoscopy for chronic diarrhoea or abdominal pain. The significance of these lesions is, however, uncertain.

We have therefore studied the characteristics of 30 consecutive patients in whom ileal aphthae were demonstrated at ileocolonoscopy. Patients were aged 23-66 yrs. (median 32.5 yrs.). 19 patients were female. The indication for ileocolonoscopy was assessment of known inflammatory bowel disease (UC n=3, CD n=8), chronic diarrhoea (n=10), abdominal pain (n=6) and rectal bleeding (n=3). 2 patients were taking non-steroidal anti-inflammatory drugs (NSAID).

Of the 19 patients without known inflammatory bowel disease, 17 had normal inflammatory parameters (haemoglobin, platelets, ESR and C-reactive protein). 2 patients had a mild rise in ESR, 1 patient had a borderline low B12 level. 4 patients had undergone small bowel barium studies and 2 had had labelled white cell scans. These tests were all normal.

No obvious morphological differences were noted in aphthous ulcers detected in patients with or without IBD or those on NSAID's. Histology of ileal biopsies showed an inflammatory infiltrate in 13 / 19 patients. Further sectioning revealed inflammation in 2 additional cases. Granulomas were absent in all cases.

Ileal aphthous ulceration may be the only abnormality detected in patients undergoing ileocolonoscopy for the investigation of gut symptoms. Morphology, histology, and additional standard investigations offer no apparent clues as to the significance of such lesions. Though a small number may be due to the use of NSAID's, the majority appear likely to represent a form of Crohn's disease. Prospective follow-up studies by ileo-colonoscopy and immuno-pathology are essential to determine the significance and natural history of these lesions.

TH155

Prospective audit of Thoracoscopic Splanchnicectomy in the management of intractable upper abdominal pain.

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AIMS: Methods used for the relief of intractable upper abdominal pain have variable success. Anecdotal reports have suggested that Thoracoscopic Splanchnicectomy (TS) may be associated with improved response rates. The aim of this study was to prospectively evaluate the short and medium term response in a consecutive series of patients undergoing this procedure.

METHODS: All patients presented with a clinical syndrome of intractable upper abdominal pain, most frequently from chronic pancreatitis refractory to standard treatment. Assessment was performed by analog pain scores and analgesic requirements with a minimum follow up of six months.

RESULTS: Six males and five females (median age 41, range(34-69)) underwent TS between June 95 and April 96. Procedure related morbidity was mild. At one month, a good response (pain score reduction of >4 and reduction in analgesia) was achieved in 8 out of 11 patients (73%) and a moderate response (pain score reduction of >2<4 and reduction in analgesia) in 1 out of 11 patients (9%). At six months, a good response was sustained in 6 out of 10 patients (60%), and a moderate response was seen in one patient (10%), one patient having died from disease progression prior to the six month follow up.

CONCLUSION: Thoracoscopic Splanchnicectomy would appear to be an effective alternative in patients with upper abdominal pain refractory to standard treatment modalities. Further prospective evaluation of this technique are ongoing.

TH156

COLONOSCOPIC ARGON PLASMA COAGULATION FOR BENIGN AND MALIGNANT RECTAL TUMOURS

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Endoscopic Nd YAG laser therapy for gastrointestinal tumours requires large capital expenditure, class 4 containment and carries a risk of perforation. Endoscopic Argon Plasma Coagulation (EAPC) is a diathermy based non-contact technique which may be as effective as laser therapy with fewer side effects.

Methods: All patients with colonic tumours treated by EAPC between July and December 1996 were studied. After initial endoscopic and histological diagnosis, patients received EAPC until satisfactory debulking of the tumour was achieved. The duration of each treatment, power used and patient tolerance were recorded for each session. Symptoms were assessed at each endoscopy session.

Results: 5 males and 3 females (mean age 79.1 ± 7.4 years) with rectal adenocarcinoma (5) or rectal villous adenoma (3) were treated. Reasons for non-operability were advanced age, co-existent medical problems or metastatic disease. The power used was 50-99W, with each session lasting a mean of 13.6 ± 6.1 minutes. Mean sedation requirements were diazepam 10.0 ± 4.6 mg, in addition to pethidine 50 mg given in 10/15 treatment sessions. Patient tolerance of the procedure was reported as good or excellent in all cases. Patients required 1-3 treatment sessions during the study period, with a mean of 4.3 ± 3.1 weeks between sessions. The symptoms of rectal bleeding and passage of mucus improved or resolved in 7 of the 8 cases. 1 patient died from metastatic disease during the study. No complications were observed.

Conclusions: EAPC in this group of patients was well tolerated, safe and resulted in useful symptomatic improvement.

TH157

TECHNIQUE, AND LONG TERM OUTCOME OF ENDOSCOPIC BALLOON DILATATION FOR PYLORIC STENOSIS.**C P Swain.** Royal London Hospital, Whitechapel, London E1 1BB.

Aim: The aim of this study was to review the technique, results and long term outcome of patients with benign pyloric stenosis treated with balloon dilatation. **Patients and Methods:** Sixteen patients were treated over a 7 year period. 15/16 were of Asian origin. The mean age was 31 (range 20-49). 9/16 were Clo test positive, 10/16 were taking omeprazole at presentation and 6/16 had been treated with triple therapy prior to initial endoscopy. Mean follow up of patients was 36 months (range 7-84). 4/16 had inpatient stays ranging from 2-8 days. 16/16 had oesophagitis and 10/16 had evidence of active duodenal ulceration at initial endoscopy. All had food in stomach, 3/16 had gastric dilatation at endoscopy. All had mid-bulbar stenosis and none had true endoscopic pyloric stenosis. The exit was found at 7 o'clock in 7/16. **Technique:** An 18 mm through the scope (TTS) balloon was used to dilate the duodenal stricture. A variety of techniques were needed to open the stenosis sufficiently to pass the TTS balloon which is poorly designed for this application. For 14/16 screening was needed. An overtube was passed and a paediatric endoscope used to place a guide-wire into the 2nd part of the duodenum. Tapered and balloon ERCP dilators were used over the wire to predilate the stricture prior to the passage of an 18 mm balloon. A large channel endoscope was used to pass the balloon. In 10 cases the balloon was inflated distal to the stricture and then pulled through and in 6 it was possible to inflate the balloon inside the stricture. **Results:** Eight patients required a single dilatation session, four needed two, three needed three and one patient needed four dilatation sessions before an endoscope could reach the second part of the duodenum. There were no perforations or deaths and no patient required surgery. Yearly endoscopic follow up indicated that the dilated stenosis could be crossed with an endoscope, that H Pylori was eradicated in all, and the symptoms of stenosis were abolished and none had recurrent ulceration at endoscopy. **Conclusion:** Although endoscopic balloon dilatation of pyloric stenosis can be technically demanding the long-term results are excellent.

TH159

FORCES EXERTED BY THE ENDOSCOPIST ON THE COLONOSCOPE DURING COLONOSCOPY. C A Mosse, T N Mills, DG Bell, C P Swain. Departments of Medical Physics, University College, Ipswich General and Royal London Hospitals.

Aim: An electronic device was designed and built for use at colonoscopy to allow measurement of the forces exerted by the clinician on the endoscope during colonoscopy. **Methods:** The device featured a handle designed in the shape of hinged split cylinder which could be locked around the endoscope but could be readily moved up and down the shaft as the colonoscopy proceeded. The handle consisted of two parts, one that gripped the scope and one that was gripped by the colonoscopist. One of the members that joined these parts together contained strain gauges arranged as a Wheatstone bridge so that the forces transmitted could be measured accurately. The device measured and recorded the twisting forces exerted during the examination as well as the push and pull applied. A computer stored the data on disk while in real time it displayed the forces graphically as two chart recorder style traces. The device was calibrated against a range of weights exerting force on a colonoscope using a pulley system and was shown to give reproducible linear measurements over the range of interest. A series of interchangeable split cylinders allowed it to be used with any size of colonoscope. It was electronically isolated from the patient. The width of the colonoscopes used varied from 11 - 16 mm diameter. **Results:** This device was used to measure the forces at colonoscopy in preliminary studies in 10 patients. **Results:** Peak forward force = 4.4 Kg, backward force = -1.2 Kg, left torque = 0.35 Kg meters, right torque = 0.9 Kg meters. Percentage time force greater than 1 Kg = 5%. Peak anal insertion force = 270g.

Conclusions: These measurements represent the first accurate measurements of the forces exerted during colonoscopy. Methods and developments which reduce the force exerted during successful colonoscopy are likely to diminish pain and reduce the risk of perforation. A knowledge of these forces may also help with the design of new instruments and models for teaching or research.

TH158

RANDOMIZED TRIAL OF ORAL SODIUM PHOSPHATE COMPARED WITH ORAL SODIUM PICOSULPHATE PREPARATION OF THE COLON FOR COLONOSCOPY. K Yoshioke; J Bates; D Morton; MRB Keighley. University Department of Surgery, Queen Elizabeth Hospital, Birmingham.

INTRODUCTION: Proper bowel cleansing is essential for colonoscopy. Sodium picosulphate is regarded by many as the standard preparation for endoscopy and elective surgery. Some colonoscopic studies suggest that oral sodium phosphate is superior to most other agents used for bowel preparation.

AIM: To compare oral sodium phosphate and oral sodium picosulphate in preparation for colonoscopy.

METHOD: One hundred and six patients who had colonoscopy were randomly allocated into two groups: patients having oral sodium phosphate 45ml twice day before investigation (n = 51) and those having oral sodium picosulphate 2 sachets the day before investigation (n = 55).

RESULTS: Linear analogue scale for patient's acceptability including abdominal pain, nausea, embarrassment, fear and fatigue showed that the score of fear was significantly greater in sodium phosphate group compared to sodium picosulphate group (p<0.02). Scoring of the faecal residue in the colon revealed that sodium phosphate was more effective in the ascending (p<0.05), descending (p<0.01) and whole colon (p<0.05) compared to the remainder. However, no significant difference was found in the observed area of the mucosa between the two groups.

CONCLUSION: These results suggest that oral sodium phosphate is well tolerated and a satisfactory agent for preparation in colonoscopy. In terms of bowel preparation sodium phosphate is superior to sodium picosulphate.

TH160

THERAPEUTIC SMALL BOWEL ENDOSCOPY. C P Swain. Royal London Hospital, Whitechapel, London E1 1BB

Aim: To assess the indications and outcome of therapeutic small bowel endoscopy. **Patients & methods:** From a series of enteroscopic examinations in 207 patients results of therapeutic enteroscopy in 50 cases were assessed. Most cases were performed without overtube or screening. **Indications & results:** **Bleeding:** Angiodysplasia of jejunum 14 (6 single, 8 multiple), bleeding diverticulum 1, amyloid 2, inoperable malignancy 2. No further bleeding occurred in 8/14 angiodysplasia and the diverticulum. Bleeding rate appeared reduced from the malignancies but not the amyloid cases. Bipolar probe was used for 11 and Nd:YAG laser for 8. The laser fiber was easier to pass through the scope to use at distal sites. In 15% of patients referred for enteroscopy for bleeding lesions accessible to the gastroscopist had been missed and were treated using the enteroscope. A bleeding duodenal ulcer, 3 gastric angiomias, linear erosions in hiatus hernia, 2 Dieulafoy ulcers and 3 watermelon stomachs were treated with bipolar or laser treatment and had no further bleeding. **Polypectomy.** 8 hamartomatous polyps were removed from the small bowel and 14 from stomach in 3 patients with Peutz Jeger syndrome. A duodenal carcinoid tumour was completely excised. **Feeding:** Feeding tubes were placed beyond the ligament of Treitz in 10 patients using a 0.35 mm, 400 cm guidewire, passing a feeding tube over the wire and then rerouting it through the nose. Direct puncture percutaneous jejunostomy with radiological assistance was used in 5 patients with gastric stasis or obstruction. **Dilatation:** Stricture dilatation with TTS hydraulic balloons was used in 3 patients, 2 for Crohn's and one for 1 patient with a low grade lymphoma. **Manometry:** An enteroscope was used to place small bowel manometry tubes in 4 patients. **Interventional cholangiography:** a pigtail stent was inserted via an enteroscopically placed guidewire into a bile-duct anastomotic stricture joining a Roux en Y loop in 1/2 patients. No fatalities, perforations or induced bleeding occurred in this series. **Conclusions:** Therapeutic enteroscopy offers effective haemostasis for a subgroup of patients with bleeding found at enteroscopy and can be used safely for a range of other therapeutic options.

TH161

PREDICTION OF RESECTABILITY OF GASTRIC TUMOURS USING ENDOSCOPIC ULTRASOUND

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The accurate assessment of the resectability of gastric tumours can be difficult using conventional imaging investigations. Posterior invasion may not be apparent on computed tomography (CT) and so patients may be subjected to inappropriate laparotomy. Endoscopic ultrasound (EUS) can clearly visualise the layers of the stomach wall and adjacent structures, including regional lymph nodes and so the locoregional staging of gastric tumours can be determined. This procedure can be performed immediately following the initial diagnostic endoscopy.

Twenty four patients with histologically proven gastric cancer underwent EUS. Eleven patients were deemed to have resectable tumours on EUS. This was confirmed at operation. Ten patients were felt to have irresectable tumours using EUS. Of these, five underwent laparotomy and palliative bypass due to extensive tumour invasion. Five patients were unfit for surgical intervention or had evidence of metastatic spread.

CT predicted resectability in 3 irresectable tumours and 5 resectable tumours but was valuable in providing information regarding metastatic spread.

Endoscopic ultrasound is more accurate than CT in predicting irresectability of gastric tumours and therefore has a valuable role in the assessment of tumours in patients who would not otherwise require palliative bypass.

TH163

TOTAL INTRAVENOUS ANAESTHESIA IN PAEDIATRIC GASTROINTESTINAL ENDOSCOPY

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Gastrointestinal endoscopy (GE) has become a useful diagnostic method for gastrointestinal diseases in childhood. In recent years, new developments in the administration of analgesic and anaesthetic drugs have greatly facilitated the technique of total intravenous anaesthesia for GE. However, this kind of anaesthesia is often associated with delay during GE.

Aim of the (pilot) study: To analyse the benefits and drawbacks of total intravenous anaesthesia during upper GE in children. **Patients:** 22 children (10 girls), mean age 7.5 years, who underwent GE because diagnostic or therapeutic purposes: 19 oesophago-gastro-duodenoscopies (GIF), of which 9 capsule-guided small bowel biopsies (DDB), and 3 percutaneous endoscopic gastrostomies (PEG). **Method:** Total intravenous anaesthesia at the discretion of the supervising anaesthetist was given to the children. The time-lag from the start of the anaesthesia to the introduction of the endoscope, the duration of the GE and the recovery time from anaesthesia were assessed. In addition blood pressure, heart rate, and SaO₂ were non-invasively monitored and automatically recorded. Anxiety before GE was independently assessed, using a scoring linear visual analogue scale from 1 to 5, by the child's parents (P), the endoscopist (E), the anaesthetist (A) and the nurses (N).

Children older than 6 years were asked to assess their own anxiety (Ch). The agitation, degree of discomfort and quality of operating conditions were assessed too.

Results:

DELAY FROM SCHEDULED TIME	Mean time-lag (minutes)	MEASUREMENTS	Mean results	ANXIETY CHILD
Start anaesthesia-introduction scope	15.59	Systolic RR	96.7 mm Hg	By A=2.6
Time GE: GIF (n=19) DDB (n=9) PEG (n=3)	18.33 12.44 28.50	Heart rate SaO ₂	109.0 p.m. 96.8%	By N=2.7 By P=2.9
Recovery	26.52	Operating conditions	Optimal	By E=3.5
Extra GE-time total	43.45	Physical restraint	Not needed	By Ch=3.6

Conclusions: Our preliminary results show a total mean extra endoscopy time of 43.45 minutes for total intravenous anaesthesia in paediatric upper GE, of which 15.6 minutes in the endoscopy room. The operating conditions were optimal. The anxiety before GE was experienced by the child as more successful than observed by the adults.

TH162

A PROSPECTIVE RANDOMISED CONTROLLED STUDY OF THE USE OF RANITIDINE IN PATIENTS WITH GASTRIC CANCER

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Introduction:-The H₂ antagonist cimetidine has been shown in one study to improve the outcome in patients suffering from gastric cancer. In this study we have examined the use of the more potent H₂ antagonist ranitidine following operation for gastric cancer. **Methods:**- We performed a multi-centre, prospective, randomised, double blind, controlled trial on 222 patients with gastric cancer who underwent radical or palliative resection or who were deemed inoperable at presentation. The patients received either ranitidine 150mg bd or placebo bd. The participating clinicians were members of the Yorkshire GI Tumour Group. The principal outcome measures were survival and survival excluding 30 day mortality. **Results:**- The median survival (95% confidence intervals) was 331 (232-393) days in the ranitidine group compared to 187 (143-269) in the placebo (p=0.225). When patients who died within 30 days of operation were excluded (21 in placebo group, 15 in the ranitidine group) the difference in survival remained not significant (p=0.358). The median survival in respect of staging is shown.

Stage	I	II	III	IVa	IVb
Placebo					
patients (n)	7	17	46	17	24
survival (days)	-	612	266	134	62
Ranitidine					
patients (n)	5	23	41	17	19
survival (days)	-	744	377	313	75
p (logrank)	-	0.69	0.28	0.073	0.88

Conclusion:- Although the outcome is better in the ranitidine group and the difference approaches significance in stage IVa, this study does not demonstrate significant benefit from the use of ranitidine in gastric cancer. Further, larger studies may be indicated.

Motility TH164-TH176

TH164

THE SPECTRUM OF ENTERIC DYSMOTILITY REVEALED BY PROLONGED SMALL BOWEL MANOMETRY. DL

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Clinical small bowel manometry (SBM) can identify differences between groups of subjects, but its diagnostic value remains uncertain. We used computer-analysed SBM in 47 studies in 18 healthy controls to construct a database of normal values of 20 variables of the migrating motor complex (MMC); the diagnostic potential of this technique was supported by a study of Chagas' disease in Brazil, in which 21/21 patients had ≥ 2 variables outside the normal range. We used prolonged SBM as a diagnostic test in 63 UK tertiary referral patients with suspected dysmotility. Subjects were studied for 24 hrs with a triple-sensor nasojejunal manometric catheter linked to a digital datalogger; data from the sensor located at the d-j flexure was used to calculate the 20 variables. SBM failed in 6 subjects (10%). Motility was judged to be normal in 17 subjects, with ≤ 1 abnormal variable. The remaining 40 patients with ≥ 2 abnormal variables (range 2 - 9, median 4) included all 14 patients with known pathology - diabetic neuropathy (5), vagotomy diarrhoea (3), scleroderma (2), enteric myopathy (3), CNS disease (1) - and 4/4 'irritable bowel' patients with refractory urgent and frequent defaecation. Abnormal records were marked by distortion, and, in 5, by abolition of the normal difference between diurnal and nocturnal activity. In 7, there was marked attenuation or absence of a motor response to food (not all patients could tolerate a normal meal). In 4, there were 'Chagas-like' prolonged Phase 3 and slow propagation of the MMC: another 7 had one or other of these abnormalities. In contrast, ultra-rapid MMC propagation was seen in 3/5 diabetics, and 2 others with diarrhoea. Low amplitude contractions were seen in 3 (scleroderma 2, dilated bowel 1) but not in patients with myopathy. 3 had MMCs by day but not at night, and 3 had excess MMCs throughout. We suggest that computer-analysed 24-hr SBM is an objective and reproducible diagnostic technique; it reveals diverse patterns of dysmotility that probably reflect different pathologies of gut muscle and nerves.

TH165

A NOVEL METHOD FOR 24 HOUR PANCOLONIC AMBULATORY MANOMETRY

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Normal colonic motility patterns have not been clearly defined. The aim of this study was to establish a new technique and describe colonic motor patterns using 24 hour ambulatory pancolonic manometry.

Five healthy volunteers were recruited to the study. Colonic motility was measured using two silicon coated catheters (OD-3mm) with 5 pressure transducers at 15cm intervals. The proximal catheter was introduced transnasally and its tip positioned at the splenic flexure under fluoroscopic control. The distal catheter was introduced transanally in an unprepared colon and its tip positioned in the descending colon with the help of a colonoscope. No sedation was used for the colonoscopy. The tip of the distal catheter was clipped to the colonic mucosa with a titanium clip. The transducers spanned the bowel from the terminal ileum to the rectum. Data was recorded continuously on a portable data logger (MMS Universal Portable System). All subjects were fully ambulant and ate their own meals.

Recordings were made for a total of 116 hours in 5 subjects. The colon exhibited high amplitude propagating contractions (HAPC), migrating motor complexes (MMC) and rectal motor complexes (RMC). Mean number of HAPC was 5.24/24hrs, 16% occurring within 1 hour of waking and 28% preceding defecation. Mean number of MMC was 11.8/24hrs, 33.5% of which propagated into the caecum. Mean number of RMC was 10.6/24hrs, 17.8% propagated aborally and 9.8% propagated orally.

The human colon exhibits phasic activity which is propagated from the terminal ileum. The rectum shows complexes which are propagated in an oral as well as aboral direction.

TH167

GASTRIC ARRHYTHMIAS IN THE FUNCTIONAL BOWEL DISORDERS.

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Cutaneous electrogastrography (EGG) abnormalities including arrhythmias and a postprandial power decrease have been described in functional dyspepsia (FD). EGG arrhythmias have been well correlated with antral dysmotility. The aim of this study was to substantiate EGG abnormalities in FD, and to compare FD patients with patients suffering from irritable bowel syndrome (IBS). **Methods:** Patients studied included 105 with dyspepsia with a normal endoscopy and abdominal ultrasound scan, 60 with IBS diagnosed by the Rome criteria and 30 healthy controls. Two cutaneous bipolar electrodes were placed over the stomach and connected to an EGG recording unit (Synectics, Stockholm, Sweden). EGG was performed according to a standard protocol which included a 2 hour pre/postprandial study. Bradygastria was defined as 0-2cpm, normal slow wave activity as 2-4cpm; and tachygastria as 4-9cpm. Postprandial power change was calculated. Statistical analysis was performed by the Student's t-test. 26 patients had a radiolabelled gastric emptying study performed to correlate EGG abnormalities with gastric emptying. Abnormal EGG was defined as <70% normal slow wave activity either preprandially or postprandially. **Results:** A postprandial power decrease was observed in 8 controls and this was not considered to be an abnormality when present alone. Two controls had <70% normal slow wave activity either preprandially or postprandially. EGG abnormalities were present in 32 (30%) FD patients and 6 (10%) IBS patients. 35 IBS patients also had dyspepsia, including all 6 patients with abnormal EGG. Mean % normal slow wave activity pre/postprandially were: controls 86.9/90.0; FD 81.6/82.9 (p<0.02); IBS 86.6/88.9. No correlation was found between EGG arrhythmias and delayed gastric emptying. **Conclusions:** 1. EGG has a high (93%) diagnostic specificity. 2. Postprandial power decrease is observed in healthy controls. 3. 30% of FD patients have abnormal EGG suggesting antral dysmotility. 4. In IBS, EGG abnormalities only occur when dyspepsia is present.

TH166

VOLITIONAL SWALLOWING MODULATES CORTICAL SWALLOWING PATHWAYS VIA BRAINSTEM MEDIATED INTERACTIONS

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Background: Swallowing is a complex process exhibiting both excitatory and inhibitory influences over the muscles of the upper digestive and respiratory tracts. Furthermore, the cortex has an important role in the initiation and modulation of swallowing and respiration. Despite these observations, the functional interactions between volitional swallowing and the cortical pathways to human swallowing and respiratory musculature are unknown. **Aims:** To determine how volitional swallowing interacts with the cortico-fugal pathways to swallowing and respiratory musculature in man. **Methods:** Swallowing musculature (Mylohyoid) and respiratory musculature (Diaphragm) were studied in 8 healthy volunteers (7 male, age range 24-32 yrs). Mylohyoid and diaphragm EMG responses to transcranial magnetic stimulation of the cortex were recorded, in maximal inspiration, at intervals of: 100 msec between 0-1 sec, 2 sec and 5 sec, after a 5ml water bolus swallow or a control task (hand contraction). **Results:** When compared to the control task, swallowing facilitated the mylohyoid responses between 0 and 0.4 sec (swallowing: 670±21µV, control: 565±36µV, p<0.02) before inhibiting them between 0.6 and 2 sec (swallowing: 460±20µV, control: 637±26µV, p<0.01). In contrast, the diaphragm responses were consistently inhibited from 0.4 sec onwards (swallowing: 150±11µV, control: 187±10µV, p<0.05). **Conclusions:** Volitional swallowing modulates the cortical pathways to human swallowing and respiratory musculature, via excitatory and inhibitory influences, a finding that reflects processing by the brainstem swallowing centre.

TH168

HISTOLOGICAL PHENOTYPING OF ENTERIC SMOOTH MUSCLE DISEASE CAUSING FUNCTIONAL INTESTINAL OBSTRUCTION IN CHILDHOOD

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Functional intestinal obstruction or chronic idiopathic intestinal pseudo-obstruction is due to defects either in the enteric innervation or in the smooth muscle.

We have studied full-thickness intestinal samples from 27 patients with functional intestinal obstruction due to enteric smooth muscle disease, using routine histology, electron microscopy, histochemical and immunohistochemical techniques to detect changes in the intestinal smooth muscle.

Two patients presenting at the age of 6 months and 18 months had an acquired intestinal myopathy as a result of an autoimmune process. In 25 the disorders were congenital, and of these 7 had segmental abnormalities limited to the rectum and distal colon and 18 a diffuse disease affecting both the small and large bowel. We identified five apparent histological phenotypes of enteric muscle disease. Three of these represent abnormalities in morphogenesis resulting in alterations in intestinal muscle layering. Two probably exemplify intrinsic myocyte defects or changes in the extracellular matrix.

Phenotyping these patients carefully is important both in devising optimal treatment and in understanding the underlying defect. Recognition of the autoimmune smooth muscle disease is helpful, since making the diagnosis influences the patient's management. The histological phenotype alludes to probable aetiology thus allowing investigation of the possible molecular and genetic defects.

TH169

INTERSTITIAL CELLS OF CAJAL (ICC) IN THE HUMAN COLON: REGIONAL DENSITY VARIATIONS

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To determine the regional variation of density of ICC in the wall of the normal human colon, we have studied 109 colonic tissue blocks.

ICC were identified in the colon by immunohistochemical staining, using a rabbit polyclonal anti-c-kit antibody (Oncogene Science). Normal colonic tissue was defined as non-involved tissue obtained at surgical resection for a non-obstructing carcinoma of the colon. The regions of interest were right, transverse and left colon. Density of ICC was graded on the basis of the number of ICC per high power field. Statistical analysis was performed using chi-squared tests.

In the myenteric plexus the transverse colon ($p=0.009$) and right colon ($p=0.05$) had a significantly higher density of ICC than the left colon. Although not statistically significant, there was a trend for the density of ICC to be higher in the transverse colon than the right colon in the myenteric plexus. In the circular muscle layer, the right colon had the highest density of ICC, this was significant in comparison to the left colon ($P=0.02$) but not the transverse colon. No significant regional variations in ICC density were identified in the longitudinal muscle layer.

Regional variations in the density of ICC are present in the colon. The highest density of ICC in the myenteric plexus was observed in the transverse colon, the proposed site of pacemaker activity.

TH170

TACHYODDIA INDEPENDENT FROM THE DUODENAL MIGRATING MOTOR COMPLEX MAY BE A PART OF SPHINCTER OF ODDI DYSFUNCTION. EA Stoner, CC Ainley, DF Evans, V Kulhali, AJK Piotrowicz. St. Bartholomew's and the Royal London School of Medicine and Dentistry, London.

Manometric measurements of the sphincter of Oddi (SO) have enabled a better understanding of its physiology and recognition of the condition of sphincter of oddi dysfunction (SOD). Presently SOD is only reliably diagnosed by an elevated basal pressure. Previously SO phasic activity has been shown to closely follow the migrating motor complexes (MMCs) with maximal frequency during phase 3 of the MMC. A raised frequency of contractions ($>8\text{cpm}$) has been termed as tachyoddia however it is not regarded as clinically significant.

Aims 1) To determine the incidence of tachyoddia. 2) To look at the relationship between tachyoddia, duodenal activity, and SOD

Methods SOM was performed using a triple lumen catheter (Wilson-Cook, USA), the central channel being continually aspirated. A station pull through technique was employed. The duodenal motility was measured using a single lumen 5 French catheter taped to the outside of the duodenoscope.

Results 65 patients with post cholecystectomy pain, idiopathic pancreatitis or biliary pain underwent SOM. 15 of the 65 (23%) patients had at least one episode of tachyoddia.

Basal pressure	Tachyoddia synchronous with MMC	Tachyoddia independent of MMC	Total
Raised	1	4	5
Normal	9	1	10
Total	10	5	15

A raised basal SO pressure is significantly associated with independent tachyoddia (Fisher's exact test $p<0.05$.)

Conclusion. The SO may have its own pacemaker which is dissociated from the control of the MMC in patients with SOD. Tachyoddia independent of the MMC should now be regarded as part of sphincter of Oddi dysfunction.

TH171

GENDER DIFFERENCES AND REPRODUCIBILITY OF WHOLE GUT VISCERAL SENSITIVITY. CY Francis, LA Houghton, PJ Whorwell. Dept of Medicine, University Hospital of South Manchester.

Abnormalities in gut visceral sensation are currently regarded as being important in the pathophysiology of functional bowel disorders. However, its inter-subject variation, its reproducibility (or intra-subject variation) and the effect of gender on these parameters has received little attention. Repeat studies on 8 healthy female (aged 20-37 yrs; median 23 yrs) and 10 healthy male (aged 20-57 yrs; median 22 yrs) volunteers were carried out to assess the sensory responses of the oesophagus [O], duodenum [D], jejunum [J], ileum [I], colon [C] and rectum [R] to isovolumic balloon distension. The order in which these regions were distended was randomised, and there were 3 to 47 weeks (median 9 weeks) between studies.

Results Female subjects tended to be more sensitive than male subjects to distension of the O [vol to discomfort (ml): females 15 (7.5-20) geometric mean (range) v males 24 (10-110); $p=0.16$], D [73 (40-110) v 99 (50-150); $p=0.08$], J [58 (40-70) v 70 (30-170); $p=0.32$], I [55(30-100) v 92 (40-150); $p=0.029$], C [177 (110-280) v 235 (150-500); $p=0.23$] and R [191 (100-400) v 211 (150-325); $p=0.58$]. Furthermore, it can be seen from the above ranges that the inter- (or between-) female variation was less than the inter-male variation; this difference reaching significance in the O ($p=0.05$) and J ($p=0.0015$). However, the intra- (or within-) female variation was not apparently different from the intra-male variation in the O [difference from 1st to 2nd study: 2.5 (0-7.5) median (range) v 5 (0-40)], D [10 (0-30) v 20 (0-50)], J [20 (20(0-30) v 30 (0-90)], I [40 (10-40) v 10 (0-70)], C [40 (10-140) v 60 (20-220)] and R [70 (0-125) v 65 (0-125)]. These male-female differences were not related to differences in anxiety between the female [HAD score, 4.5 (0-8) median (range)] and male [5.0 (3-9); $p=0.41$] volunteers.

Conclusion Because males are less sensitive and have a wider inter-subject variation than females, they may be less prone to abnormalities in visceral sensation following exposure to noxious stimuli. This might help to explain the preponderance of female to male patients with functional bowel disorders.

TH172

GASTRIC EMPTYING (GE) AND GASTROINTESTINAL REGULATORY PEPTIDES (GRP) IN CHILDREN WITH RECURRENT EPIGASTRIC PAIN (REP)

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Recurrent epigastric pain is often of uncertain aetiology and it is therefore attributed to psychological causes. Gastrointestinal motility disorders have been implicated in the pathogenesis of abdominal pain and regulatory enteropeptides, in the pathogenesis of intestinal dysmotility. However, the incidence of gastric dysmotility and the role of GRP in children with REP are poorly defined. We therefore, carried out a prospective study in 36 children (mean age 10.4 years, 18 males) with REP of uncertain aetiology, in order to detect the incidence of gastric dysmotility and the role of serum motilin. In 28 patients, REP were associated with non-ulcer dyspepsia: early satiety, postprandial abdominal bloating and/or distention. In 8, REP was paroxysmal, precipitated by prolonged fasting. Seventeen patients (47%) were found to have abnormal gastric emptying assessed by gastric scintigraphic studies: 12 (43%) of the 28 patients with dyspepsia (mean age 9.4 yrs) were found to have delayed emptying of a solid meal (mean $T_{1/2}$ of 50% of ^{99m}Tc -phytate in stomach was 147.2 minutes); 5 of the 8 (62%) patients with paroxysmal pain (mean age 13.4 yrs) had rapid gastric emptying (mean $T_{1/2}$ of 50% of ^{99m}Tc -phytate in stomach was 55 minutes). Fasting serum motilin concentrations were lower in the patients with REP compared with 26 healthy controls ($p<0.0001$). However, no significant correlations were found between serum motilin concentrations and the duration or the severity of REP or gastric emptying time. The treatment with cisapride and/or erythromycin was associated with resolution of symptoms in all of the patients with delayed gastric emptying. Similarly, dietary modifications were associated with a relief in symptoms in children with rapid gastric emptying. In conclusion, GE abnormalities are common in children with REP of uncertain aetiology. The role of GRP in children with REP should be further investigated.

TH173

THE USE OF RADIOTRANSMITTING CAPSULES TO MEASURE INTESTINAL TRANSIT *SJ Lewis* and *KW Heaton*. Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW.

Because luminal pH increases as the duodenum is entered then falls on entry into the caecum, the pH radiotransmitting capsule can be used to measure small bowel transit-time. It can also be used to measure whole-gut transit-time (WGTT) and, by subtraction colonic transit-time. However the latter is a valid exercise only if WGTT is not itself altered by the capsule.

We set out to see if WGTT measured by the pH radiotransmitting capsules differed from WGTT measured simultaneously using the traditional barium impregnated plastic pellet method.

13 healthy volunteers had their WGTT measured using plastic marker pellets of different shapes, then collecting two stool samples and x-raying them. At the same time a pH radiotransmitting capsule was swallowed and tracked. These measurements were then repeated with the volunteers taking in order wheat bran, senna then loperamide in maximally tolerated amounts.

No significant differences were seen between the two sets of measurements on baseline diet or if the intestinal transit was altered using wheat bran, senna or loperamide.

Median WGTT (h) and IQ range using the plastic pellets and a pH capsule

	n	Pellets	Capsule	95% CI
Baseline	37	63	55	36, 76
Wheat bran	13	39	42	31, 58
Senna	13	41	42	36, 57
Loperamide	11	74	78	67, 113

We found no systematic difference in measured WGTT between results with the traditional plastic marker pellets and with the pH radiotransmitting capsule. This was true even if WGTT was artificially increased or decreased. In addition the pH radiotransmitting capsule gives information on small bowel transit and caecal anal transit-times, thus negating the need to use separate techniques for each or the use of radioactive isotopes. This pH radiotransmitting capsules may be a useful method of assessing small and large intestinal transit-times.

TH175

ALOSETRON SLOWS COLONIC TRANSIT IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS) *JM Foster*, LA Houghton, PJ Whorwell. Department of Medicine, University Hospital of South Manchester, M20 2LR, UK

The selective 5HT₂ antagonist, alosetron reduces abdominal pain/discomfort in patients with IBS (Bardhan et al, Gastroenterol 1996;110:630) and slows whole gut and colonic transit in healthy volunteers (Houghton et al, Gastroenterol 1995;108:864). However, its effect on gastrointestinal transit in patients with IBS has not been previously investigated. Twelve IBS patients (aged 23-56 yrs) diagnosed by the Rome criteria, were therefore entered into a randomised, double blind, crossover study, comparing the effects of oral alosetron (2mg bd x 8 days) with placebo on whole gut (mouth to anus), small bowel (mouth to caecum) and colonic transit. Mean whole gut transit (MWGT) was determined by the number and time of excretion of 3 different radio-opaque markers ingested on 3 consecutive days (days 2, 3 and 4). Small bowel transit (SBT) was measured as the time from ingestion of a standard meal of mashed potato, sausages and beans (non-absorbable carbohydrate) to a rise in breath hydrogen of 3 ppm sustained for 30 min (day 5). Colonic (CT), left colonic (LCT), right colonic (RCT) and rectosigmoid (RST) transit were evaluated by abdominal X-ray (day 5).

Results

	Placebo	Alosetron	P
WGT (marker 1; hrs)	68(21-125)	82(14-159)	0.09
WGT (marker 2; hrs)	67(16-137)	73(24-144)	0.07*
WGT (marker 3; hrs)	52(16-119)	54(13-120)	0.47
MWGT (hrs)	59(18-114)	72(20-141)	0.13
SBT (min)	335(190-490)	330(200-510)	0.51
CT (hrs)	38(1-67)	49(1-72)	0.07*
LCT (hrs)	12(0-23)	23(0-52)	0.006*
RCT (hrs)	7(1-23)	7(0-31)	0.57
RST (hrs)	8(0-24)	5(0-23)	0.38

Results expressed as median (range)

Conclusion Alosetron delays colonic transit by prolonging left colonic transit. These results add further to the body of evidence that alosetron may have a therapeutic role in irritable bowel syndrome. "This research was funded by GlaxoWellcome, UK."

TH174

SUMATRIPTAN AT A THERAPEUTIC DOSE ALTERS OESOPHAGEAL MOTILITY. *JM Foster*, LA Houghton, PJ Whorwell. Dept of Medicine, University Hospital of South Manchester.

3-5% of patients taking the 5HT_{1D} agonist sumatriptan (S) for migraine experience chest discomfort, potentially suggesting a cardiac origin. However, we have recently suggested that the oesophagus may be the cause of this chest discomfort, as a suprathreshold dose of S (16mg, sc) significantly alters oesophageal motility without affecting the ECG. The aim of this study was to investigate whether a therapeutic dose of S (6mg, sc) also affects oesophageal motility. Lower oesophageal sphincter (LOS), oesophageal body (4 sites), gastric and pharyngeal (to monitor swallows) pressures were recorded using a perfused manometric catheter with sleeve sensor in 16 healthy volunteers (aged 19-32 yrs; 9 male) before and after administration of S or saline control. Sequences of 6 consecutive 5ml water swallows with a minimum interval of 20 sec between each swallow, were carried out -15, -5, 5, 15, 30, 45, 60, 80, 100, 120, 150 and 180 min post-injection. Treatment order was randomised and double-blind; throughout the study ECG and symptoms were monitored. **Results** S significantly increased the amplitude of oesophageal contractions (mean increase from pre-injection: S 4.8mmHg, placebo 4.5mmHg; difference 9.3mmHg, 95%CI 4.1-14.5mmHg, p=0.002); an effect that was maintained throughout the whole of the 3 hr recording period. In addition, S induced a transient increase in LOS pressure immediately after injection (S 10.9mmHg, placebo 5.1mmHg; difference 5.8mmHg, -0.7-12.3mmHg), although it had no overall effect on LOS pressure over the time period studied (S 1.9mmHg, placebo 2.1mmHg; difference 0.2mmHg, -3.9-4.2mmHg). S, however, did not affect the duration (S 0.3s, placebo -0.1s; difference 0.4s, 0.2-0.5s) or velocity of propagation (S -0.09 cm/s, placebo -0.12cm/s; difference 0.03 cm/s, -0.15-0.21 cm/s) of oesophageal contractions. Chest discomfort was only experienced in one subject and although this subject did show a change in oesophageal motility, there was no correlation with the degree of change. No subject exhibited any ECG abnormalities. **Conclusion** At therapeutic doses S also has an effect on oesophageal motor function, and this provides further evidence of a possible oesophageal cause of S-induced chest symptoms.

TH176

GASTRIC EMPTYING IN HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTED INDIVIDUALS: RELATIONSHIP TO SYMPTOMS, AUTONOMIC FUNCTION AND GASTROINTESTINAL (GI) PATHOGENS. *PJ Neild*, R Jewkes, BG Gazzard. Chelsea and Westminster Hospital, London, U.K.

Symptoms suggestive of delayed gastric emptying are common in HIVseropositive (HIV+) individuals, as is autonomic neuropathy, though often subclinical. We tested the hypothesis that GI symptoms may be related to objective delay in gastric emptying and that this may be associated with autonomic dysfunction and/or the presence of opportunistic GI pathogens. **Methods:** 19 HIV+ subjects with enteric infections (HIV/P) and 37 HIV+ subjects with no identifiable pathogens (HIV/NP) were compared with 12 presumed HIV-ve healthy controls (cont). Subjects completed a symptom score and underwent a series of autonomic function tests (aft), and a scintigraphic solid gastric emptying test, using a single headed gamma camera with anterior and posterior views. **Results:** Gastric half emptying time (t_{1/2}) was increased in HIV+ subjects and significantly so in those with GI pathogens, though lag phase (t_{lag}) and the proximal emptying component (pt_{1/2}/ t_{1/2}) were less affected. GI symptoms and autonomic dysfunction were significantly increased in HIV+ subjects compared with controls but did not correlate with gastric emptying (r²=0.021 and 0.012 respectively). t_{1/2} was related to CD4 count (r²=0.13, p=0.006) and %weight loss (r²=0.21, p=0.0004).

results expressed as mean±SEM	cont	HIV+NP	HIV+P
symptom score/15	0.08±0.08	5.34±0.63**	6.9±0.86**
SD of R-R intervals (SDRR) (ms)	61.56±4.12	39.95±3.8*	33.29±4.31**
gastric t _{1/2} (min.)	66.9±5.16	92.38±8.04^^	158.3±20.9**
t _{lag} (min.)	22.08±3.54	29.08±3.02	48.5±9.42
pt _{1/2} / t _{1/2}	0.75±0.05	0.63±0.03	0.60±0.03

*p<0.05, **p<0.01, ^^p<0.001 wrt cont. ^^p<0.001 wrt HIV/P

Conclusions: Gastric emptying is disturbed in a number of HIV+ subjects, particularly those with small intestinal GI pathogens, but neither gastric symptoms or autonomic dysfunction can predict those with abnormalities. Delay may result from local production of cytokines, eg tumour necrosis factor alpha, or duodenal dysmotility causing reflex inhibition of emptying.