Helicobacter pylori W1-W11

W1

INTRAFAMILIAL CLUSTERING OF *HELICOBACTER PYLORI* STRAINS AND CORRELATION OF VIRULENCE WITH DISEASE ACTIVITYSK Vyas¹, RJ Owen², PR Hawtin¹ (introduced by MJP Arthur)
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Recent reports of *H. pylori* survival in faeces and the mouth suggest the possibility of enteral transmission while sero-epidemiological studies have highlighted the importance of childhood in acquiring this chronic infection. Although the severity of disease may depend on differences in host susceptibility, the proposal for a single ulcerogenic strain is contentious. We investigated a three generation family for *H. pylori* strain heterogeneity, intrafamilial clustering and endoscopic abnormality.

Upper gastrointestinal symptoms and treatment were recorded. Infection was determined by ¹³C-urea breath test and serology (ELISA:acid-extracted antigen:NCTC11638). All positive individuals consented to endoscopy and antral biopsies for culture and histology. Strains were characterized using RFLP of HaeIII restriction digests of the PCR products of urease A and B genes recovered from each individual and immunoblotting for the *cagA* product which is closely associated to duodenal ulceration.

Of twenty-three subjects screened, 13 were seropositive of whom 11 were confirmed by ¹³C-urea breath test. Endoscopy in these 11 subjects revealed duodenal ulceration in 7 with co-existing oesophagitis and gastric ulceration in one. One had gastric ulceration alone and another had severe oesophagitis alone. Genotypic analysis revealed clustering amongst first degree relatives. Active duodenal ulceration was not strain specific but all subjects with duodenal ulceration demonstrated immunoreactivity to the putative *cagA* product.

These results identify clustering of *H. pylori* strains amongst first degree relatives. Furthermore the presence of duodenal ulceration with genotypically heterogeneous strains associated with the *cagA* product suggests a possible pathogenic role for this protein. Finally, this study repudiates the proposal for a single ulcerogenic strain as defined by PCR-RFLP.

W3

A NEW RAPID WHOLE BLOOD TEST FOR *HELICOBACTER PYLORI* ANTIBODIES COULD REDUCE DIAGNOSTIC OESOPHAGO-GASTRODUODENOSCOPY (OGD) IN PATIENTS WITH DYSPEPSIA.

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In the absence of *Helicobacter pylori* antibodies (Hp abs) peptic ulcer disease and gastric cancer is unlikely (Sobala et al 1991). We have tested a new rapid whole blood test (RWBT) (Helisal Test, Cortecs) for the detection of Hp abs. Validation of this test by one of us and others has shown 83.3% specificity and 91.4% sensitivity. The RWBT can be performed in the consulting room and gives a result in less than five minutes.

We have compared Hp abs status by RWBT with blinded OGD findings in 42 untreated patients with dyspepsia (19 males, 23 females; age range 19-95, mean 55.3±18.9 years)

Twenty three patients were Hp abs -ve and OGD findings were normal in 8, reflux oesophagitis (RO) in 8, GU in none, gastritis in 4, DU in none, duodenitis in 3, and gastric cancer in none. Nineteen patients were Hp abs +ve and OGD findings were normal in 4, RO in 2, GU in 3, gastritis in 1, DU in 5, duodenitis in 3 and gastric cancer in 1. The diagnostic rate for peptic ulcer was different between the two groups (none of 23 versus 8 of 19, P=0.00128 Fisher's exact test), other diagnostic rates were not different.

This small study suggests that the RWBT may be used to direct OGD to those patients at greater risk of peptic ulcer disease; Hp abs -ve patients could be offered symptomatic treatment without investigation in the absence of other indications.

W4

A SIMPLE 3 MINUTE LATEX AGGLUTINATION TEST FOR RAPID *H. PYLORI* SERODIAGNOSIS

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Introduction:

A serological response to *H. pylori* provides a convenient non-invasive method for diagnosis. The current available kits assess the immune response by ELISA. This has the disadvantage of requiring expertise, laboratory space with equipment and for efficiency batch testing of serum. A latex agglutination test has been developed (Oxoid, Unipath Limited) which requires no expertise or specific equipment. By using a serum sample a result is available in 3 minutes.

Methods:

To assess the latex agglutination test 202 consecutive patients attending endoscopy were studied. At endoscopy antral and body biopsies were obtained for histology and urease testing and 5 ml blood taken. The biopsies were assessed blind by two pathologists used to identifying *H. pylori* by both H&E and modified giemsa stains.

Results:

Out of 192 serology samples 90 patients were positive by histology and urease testing. The latex agglutination test was quick and easy to use and produced a sensitivity of 86% with a specificity of 75% and a positive predictive value of 85% all within 4% of a commercial ELISA assay (Helico G, Porton).

Conclusion:

The sensitivity and specificity of the Oxoid agglutination test is equivalent to that of a commercial ELISA. Unlike the ELISA assay the agglutination test would be inconvenient for large number of samples. It has the advantage of being very simple and quick to use without specialist equipment. The Oxoid agglutination test would be ideal to use in out-patients or general practice and will help facilitate patient management.

WHO GETS FALSE-NEGATIVE *H. PYLORI*(Hp) ELISA RESULTS? Mathialagan R, Loizou S, Beales ILP, Scunes D, Calam J. Hammersmith Hospital, London.

We developed an in-house ELISA for IgG to Hp using a method published by others. Concordance with a commercial ELISA was >90%, but its sensitivity was only 76% against endoscopic diagnosis. As clinical decisions are being based on similar tests we asked: Which patients give a false negative result?

Methods: A combined antigen preparation from aqueous extraction of 5 different strains was used at 15 µg protein/ well in 96 well plates. Serum was diluted 1:1000 and tested in duplicate. Goat anti-human IgG conjugated to alkaline phosphatase was then applied at 1:4000. Previously determined cut off points of: >50 units-positive & < 30 units-negative gave a specificity of 97%, but the sensitivity varied between patient groups. 116 patients were studied. Hp infection was diagnosed by rapid urease test, culture and histology of antral biopsies. We identified patients in the following groups (i) Hp and active duodenal ulcer (DU) (mean age 50.8±13.4), (ii) Hp and atrophy or intestinal metaplasia of the antrum or body but no ulcer (atrophy group) (age 53.5±12.7), (iii) Hp with neither ulcer nor atrophic gastritis (age 50±10.2) (iv) uninfected (age 42.5±13.3).

Results: Of 83 patients found to be infected at endoscopy 21(24%) gave negative ELISA results. Of patients in groups (i-iii), false-negative results were found in 0/19 (0%) with active DUs, but 13/22 (59%) of those in the atrophy group, and 5/33 (15%) of infected patients with neither ulcer nor atrophy. Only 1/33(3%) of uninfected patients gave a positive result.

Conclusions

Our ELISA correctly diagnosed Hp infection in all our DU patients but gave false-negative results in over half of patients with atrophic gastritis. Tests of this sort are unlikely to miss infection in DU patients but may do so in patients with atrophy who are at risk of gastric cancer.

W2

W5

A PROSPECTIVE TRIAL OF SCREENING DYSPEPSIA USING *H. PYLORI* SEROLOGY. P. Patel, M.A. Mendall, S. Khulusi, R. Lloyd, N. Molineaux, J. Levy JD Maxwell & T.C. Northfield. Dept. of Medicine St. George's Hospital Medical School, London, UK.

Background The demand for endoscopies is rising even though the majority show no visible abnormalities. A screening strategy in the under 45s using serology has been reported to save over a third of upper GI endoscopies without missing serious pathology. However, this strategy might result in persistent symptoms in those not endoscoped. **Aim** To prospectively screen dyspeptic patients under 45 using *H. pylori* serology, and a history of regular NSAIDs or sinister symptoms (BSGE guidelines); and to assess subsequent symptoms and medication in patients who are not endoscoped. **Subjects & Methods** 146 consecutive, dyspeptic patients (80 male and 66 female, between the ages of 16 and 45 years) referred for open access endoscopy were screened. A validated questionnaire was administered to assess symptoms and medication. Serum was taken and *H. pylori* IgG titre was assessed using the Helico-G ELISA. Seropositive patients (>6.3U/ml) or those who either took regular NSAIDs, or had sinister symptoms were endoscoped. The remainder were returned to their GP for symptomatic treatment and were reassessed using a questionnaire at 6 months.

Results 93/146(64%) patients were invited for endoscopy and 53/146(36%) were returned to their GP for management: Patient diagnoses (%) were as follows:

Normal DU	GU	Duodenitis	Ca	Oesohagitis
55(59)	23(25)	3(4)	4(4)	0(0)
				8(8)

Of 53(36%) patients who were not endoscoped, 45(85%) returned their questionnaire at the 6/12 reassessment. Compared to a 6/12 period prior to screening, during the 6 months after: score for severity of symptoms(p=0.02) and interference with life events(p=0.01) was reduced; GP visits(p=0.0015), days off work(p=0.05) and use of medication declined(p=0.003). Only 3 patients initially screened out were subsequently referred to a specialist for endoscopy, but all had normal findings. Total endoscopies saved was 50/146(34%).

Conclusion Prospective screening of dyspeptic patients under 45 with *H. pylori* serology is viable and saves 34% of endoscopies. Those who are not endoscoped feel better 6 months after screening even though intake of medication is reduced. This strategy could be useful for GPs when deciding who to refer for endoscopy.

W6

THE GLASGOW DYSPEPSIA SEVERITY SCORE - A NEW TOOL FOR MEASURING THE CLINICAL AND PERSONAL IMPACT OF DYSPEPSIA
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There is currently no reliable tool for providing a global measurement of the severity of dyspepsia in patients with a variety of upper GI disorders. We have designed a questionnaire for recording frequency and severity of symptoms, time off work, frequency of medical consultations, clinical investigations and use of over-the-counter and prescribed medications. Each section is scored on a sliding scale with a maximum total score of 21. We have now assessed this questionnaire with respect to reproducibility, validity, responsiveness and performance time.

- 1. REPRODUCIBILITY:** One author interviewed 50 subjects (25 males) including 20 normals and 30 with a variety of upper GI pathologies. The interview was repeated again a week later by the same author who was blinded to the dyspeptic score for the first interview. The second author who was blinded to the diagnoses and subject identity scored all the questionnaires. The mean dyspeptic score was 7.70 on Day 1 and was similar at 7.72 on Day 2. The co-efficient of variation between Days 1 and 2 was 2%.
- 2. VALIDITY:** This was assessed by comparing the dyspepsia scores in healthy volunteers and patients with upper GI diseases. The mean score in 60 healthy volunteers was 1.6 (range 0 - 8) and was significantly higher in 27 DU patients (mean score 11, range: 4-16) and 11 NUD patients (mean score 12.7, range: 9-18) (p<0.001 for both vs healthy volunteers).
- 3. RESPONSIVENESS:** Dyspepsia scores were compared before and after eradication of *Helicobacter pylori* infection in 10 DU patients. The mean dyspepsia score before eradication was 11.3 (range: 7-16) and fell to 1.8 (range: 0-9) after eradication (p<0.008).
- 4. PERFORMANCE TIME:** The mean time taken to complete the questionnaire was 3.5 minutes (range: 3-5 minutes).

CONCLUSIONS: This new questionnaire for assessing the severity of dyspepsia is highly reproducible and has high validity and responsiveness. In addition, it is simple and rapid to perform. It provides a valuable tool for assessing the response to treatment in patients with dyspepsia.

W7

THE EFFECT OF *HELICOBACTER PYLORI* ERADICATION ON THE WELL-BEING OF PATIENTS WITH PEPTIC ULCER.
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Introduction: Evidence is now compelling that relapse rates in peptic ulceration are greatly improved when *H. pylori* is eradicated. It is usually assumed that improved relapse rates equate with better health, but this has not been shown. If, for instance, the ulcer was an incidental finding in an unrelated disorder such as irritable bowel or gastric reflux, its cure would not change symptoms.

Aim: We sought to investigate the health of peptic ulcer patients following treatment to eradicate *H. pylori* and to compare the outcome of those in whom the organism was eradicated with those in whom it persisted.

Methods: Parallel questionnaires were sent to DU and GU patients in whom the outcome of eradication therapy was known, and to their GPs. We asked about symptoms and their frequency; medication; GP consultations; work; lifestyle and subjective sense of ulcer cure.

Results: 207 patients (175 DU, 26 GU, 3 both, 3 unspecified) were sent questionnaires. Median follow-up was 250(range 85-877) days, median age 54(22-84) yrs. Hp-eradicated patients (HPEs) made up 77% of 207 and Hp-persisted patients (HPPs) 23%. Replies were received from 129/159(81%) of HPEs and 137/159(86%) of their GPs (HPE-GPs), and from 27/48(56%) HPPs and 39/48(81%) HPP-GPs. Amongst HPEs, 24/127(19%) currently suffered ulcer pain compared with 14/27(52%) HPPs (p<0.001, χ^2). Of HPEs, 39/122(32%) had had one or more 'flare-ups' of symptoms during follow-up compared with 18/27(67%) HPPs (p<0.001). Doctors' responses showed 30/127(21%) HPEs had had prescriptions for their ulcer compared with 25/39(64%) of HPPs (p<0.001), while of HPEs 26/137(19%) had consulted again since eradication treatment was given, as against 25/39(64%) of HPPs(p<0.005). Of those in work 3/58(5%) of HPEs claimed to have had time off work as a result of their ulcer compared with 4/12(33%) of HPPs(p<0.02). Of the HPP group, 11/26(42%) claimed an effect on their lifestyle caused by their ulcer, compared with 15/117(13%) of the HPEs (p<0.01). Both patients and GPs were asked if they thought the ulcer was cured: 102/121(84%) HPEs and 103/116(89%) HPE-GPs thought it was, compared with 9/26(35%) of HPPs and 19/36(53%) HPP-GPs (p<0.001).

Conclusions: *Helicobacter pylori* eradication reduces prescribing, consultation rates and lost worktime, and improves symptoms in patients with peptic ulcer.

W8

TREATMENT OF *HELICOBACTER PYLORI* INFECTION - RELATIONSHIP BETWEEN INITIAL ERADICATION RATE AND THE OBSERVED 'RE-INFECTION' RATE SIX MONTHS POST TREATMENT.

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Background
The observed 're-infection' rate following apparently successful eradication of *H. pylori* infection has varied in different studies from 0% to over 45%. We have used the 14C-urea breath test (UBT) to monitor initial eradication rates as well as subsequent re-infection/late recrudescence following a large number of different candidate anti-helicobacter therapies.

Results
From October 1986 to April 1994 our group has apparently successfully eradicated the infection from 861 patients using the criteria of a negative UBT taken at least one month post treatment. We have observed 47 're-infections' of which 40 (85.1%) have occurred by 6 months post treatment.

We have arbitrarily divided our 861 eradication 'successes' into 6 different groups depending on the initial eradication rate of the anti-helicobacter therapy they received :-a) 20% or less b) 20-40% c) 40-60% d) 60-80% e) 80-90% and f) 90-100%. The observed 're-infection' rates at 6 months were a) 36.8% b) 16.7% c) 14.3% d) 5.9% e) 3.0% and f) 1.4%.

Conclusions
There was thus a strong negative correlation (-0.9567) between initial *H. pylori* eradication rate and subsequent 're-infection' at 6 months strongly suggesting that in the UK in adults most re-infections are in fact a late recrudescence of a suppressed infection and that with effective eradication therapy the true re-infection rate is very low.

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W9

EFFECT OF *HELICOBACTER PYLORI* ERADICATION ON DUODENOGASTRIC REFLUX. ¹SD Ladas, ¹J Katsogridakis, ³H Malamou, ²H Giannopoulou, ²M Kesse-Elia, ¹SA Raptis. ¹Gastroenterology Unit - 2nd Dept of Intern Med, Athens University, ²Dept of Nuclear Med, Evangelismos Hospital, Athens, ³Dept of Clin Microbiology, Penteli Children's Hospital, P Penteli, Greece.

Background. We have recently shown that in the non-operated stomach duodenogastric reflux (DGR) is usually associated with *H. pylori* colonization of the antral mucosa. Duodenal contents have a noxious effect on the gastric mucosa and may be implicated in the pathogenesis of *H. pylori* gastritis. **Hypothesis.** Is *H. pylori* colonization of the antral mucosa and DGR independent phenomena or there is a causative relationship? **Patients.** Phase one, included 29 patients aged 49±17 years. Phase two included 10/29 (age 46±19 years) phase one patients. **Methods.** Phase one: Antral biopsies were taken from each patient to investigate *H. pylori* colonization. In addition, the patient had a BrIDA-Tc-99m-In-111-DTPA scintigraphy to quantify DGR. Phase two: Patients who had both DGR and *H. pylori* colonization of the antrum were treated with Amoxycillin (1 g/day) and Metronidazole (1.5 g/day) for 7 days and a Bismuth salt (De-Nol) (4 tablets/day) for 4 weeks. Phase one was repeated at six months. **Results.** Phase one: Only 8 (44%) of those patients who had not DGR were *H. pylori*-positive, but 10 (91%) out of the 11 patients who had DGR (reflux % 11.6±9.2) were *H. pylori*-positive ($\chi^2 = 7.2$, $p < 0.01$). Phase two: Out of the 10 patients who had DGR and submitted to *H. pylori* eradication treatment, 3 were still colonized by *H. pylori*, one lost to follow up and six became *H. pylori*-negative at six months. In these six patients DGR was significantly reduced from 14.3±10.9% to 3.3±3.8% following successful *H. pylori* eradication (two tail, pair- $t = 2.6$, $p < 0.02$). **Conclusions.** Our data support recent observations suggesting that *H. pylori* may decrease antroduodenal motility, inducing DGR. *H. pylori* induced DGR may be implicated in the pathogenesis of *H. pylori* gastritis and carcinogenesis.

W11

REACTIVE OXYGEN SPECIES DAMAGE IN *H. PYLORI* GASTRITIS. I M Drake, D Warland, C S Schorah, A T R Axon, K L M White. Centre for Digestive Diseases, The General Infirmary at Leeds, UK.

Introduction Reactive oxygen species (ROS) have been demonstrated by chemiluminescence in *H. pylori* gastritis, but this does not necessarily mean they have a pathological role and cause cell damage. We measured malondialdehyde equivalents (MDA) to assess ROS-mediated lipid peroxidation in *H. Pylori* gastritis.

Patients and Methods 88 subjects were recruited for patients undergoing endoscopy for dyspepsia. 4 antral biopsies were taken, 2 for histology and 2 for MDA assay using the thiobarbituric acid technique.

Results

Histology	No. patients	Median MDA (nmol/g)
Chronic gastritis	67	143.7
Normal	13	73.5
Chemical gastritis	8	69.6
<i>H. pylori</i> present	42	164.0
<i>H. pylori</i> absent	46	88.4

MDA levels were higher in chronic gastritis than in normal histology ($p < 0.0001$) or in chemical gastritis ($p < 0.001$). There was no difference between levels in the chemical gastritis and normal group ($p = 0.49$). Patients with *H. pylori* had higher MDA levels than those without ($p < 0.0001$) and of those patients with gastritis, those with *H. pylori* had higher MDA concentrations than those without ($p < 0.001$).

Conclusions There is lipid damage attributable to ROS in chronic gastritis, and this is further increased if *H. pylori* is present. This would support a pathological role for ROS in *H. pylori* gastritis.

W10

THE PREVALENCE OF PARIETAL CELLS IN THE DUODENUM AND THEIR RELATIONSHIP TO *HELICOBACTER PYLORI* (Hp) INFECTION.

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Acid secretion in the duodenal bulb has been demonstrated, but its source has not been identified. The aim of this study was to identify parietal cells in the duodenal bulb using a novel technique to determine their prevalence.

Methods: 19 Hp+ DU (6 female, mean age 37, range 22-58) & 7 Hp- healthy controls (4 female, mean age 32, range 27-39) were studied. Hp status was determined by histology & culture of antrum & body biopsies & by ¹³C-urea breath test. Duodenal bulb biopsies were taken from all quadrants, fixed & paraffin processed. Sections were cut at 2 µm & stained with highly specific & sensitive monoclonal antibody (Mab) to H⁺,K⁺-ATPase (HK12.18, kindly donated by Dr Adam Smolka, USA) using the Avidin-Biotin technique, at a dilution of 1:2500 & incubated overnight at +4°C. The presence or absence of parietal cells was assessed by an experienced blinded histopathologist (MMW).

Results: Parietal cells were seen in 7/19 (37%) Hp+ DU & 3/7 (43%) Hp- controls.

Conclusion: Using a Mab to H⁺,K⁺-ATPase, the overall prevalence of parietal cells in the duodenal bulb (38%) is markedly higher than a previous H&E endoscopic study (< 2%). There is no difference in the prevalence of parietal cells in the duodenal bulb between Hp+ DU patients & Hp-healthy controls.

AWH is supported by a grant from Lederle Laboratories, UK.

Coeliac disease and nutrition W12-W21

W12

IgA ANTI-ENDOMYSIAL ANTIBODY IS SUPERIOR TO THE ⁵¹Cr-EDTA:¹⁴C-MANNITOL INTESTINAL PERMEABILITY TEST IN THE DIAGNOSIS OF COELIAC DISEASE.

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Coeliac disease (CD) may be under-diagnosed because of the non-specific nature of the presenting symptoms. Serological markers such as IgA R1 anti-reticulin (ARA), IgA anti-gliadin (AGA) and IgA anti-endomysial (AEA) antibodies have been advocated in the detection of such cases and may be useful in screening for silent or latent CD. Sensitivities and specificities for these antibodies, however, vary widely from centre to centre. The intestinal permeability test has been used to assess the absorptive capacity of the small intestine and is considered to be a sensitive test that distinguishes patients with CD from healthy controls and may also indicate latency. We compared permeability using a ⁵¹Cr-EDTA:¹⁴C-mannitol sugar absorption test with serology in 40 adults investigated for CD in a gastroenterology clinic over a one year period to establish which test had the greatest diagnostic power prior to subsequent confirmatory small bowel biopsy.

10 of the cases were investigated following an incidental finding of ARA on an auto-antibody screen and CD was subsequently confirmed histologically on every occasion. ¹⁴C-mannitol was more reliable in detecting CD than ⁵¹Cr-EDTA alone and, in addition, detected 5 of 8 non-CD cases with abnormal small bowel histology and negative serology. 2 cases presenting with atypical symptoms had subtotal villous atrophy despite normal permeability, one of which tested positive for AEA. Each of the 5 tests used alone gave at least one false positive and/or false negative result. Our sensitivity/specificity data for the individual tests in the diagnosis of CD is as follows:

⁵¹ Cr-EDTA	80%/66%
¹⁴ C-mannitol	97%/80%
ARA	40%/100%
AGA	90%/83%
AEA	100%/95%

In conclusion, serological testing with AEA appears to be superior to intestinal permeability testing in the diagnosis of CD. The latter test, which has been considered to reflect the functional integrity of the mucosal surface, may in fact fail to identify some patients with subtotal villous atrophy.

W13

LOW OR NEGATIVE ANTIGLIADIN ANTIBODY MAY ALSO INDICATE DISEASE

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Patients with coeliac disease (CD) may not have detectable serum IgA anti gliadin or endomysial antibodies (AGA, EMA) if serum IgA deficiency is present. To determine the significance of this problem in clinical practice, we routinely obtained small bowel biopsies and measured AGA/EMA and total serum immunoglobulin levels (IgA, IgG, IgM) in all patients suspected of having CD. EMA was detected by indirect immunofluorescence and AGA measured using a commercially available ELISA kit with levels expressed as ELISA units (EU).

We studied 130 patients, of whom 19 (15%) had villous atrophy on biopsy. Thirty-seven (28%) had low AGA (0-9 EU). Five of these (14%) had low IgA (<0.8 g/l): in three the IgA deficiency was selective and two also had abnormalities of IgG/IgM, one with a paraproteinaemia. Two patients with low AGA had villous atrophy, one with normal IgA and one with selective IgA deficiency; both were EMA negative. The remaining 17 (89%) patients with villous atrophy had AGA ranging from 43 to 645 EU and all were EMA positive.

Compared with our patients, a control group of 443 blood donors was significantly more likely to have AGA in the range 10-39 EU (261/443, 59% v. 34/130, 26%; $p<0.001$) and less likely to have AGA ≥ 40 EU (63/443, 14% v. 59/130, 45%; $p<0.001$). However, a similar proportion (119/443, 27%) had AGA in the range 0-9 EU.

In conclusion, low serum IgA AGA is common but in a symptomatic population may indicate low total serum IgA. Immunoglobulin levels should be routinely measured if AGA level measured by ELISA is low in order to identify IgA deficiency which may serologically "mask" CD or provide another explanation for symptoms.

W15

NEUROLOGICAL COMPLICATIONS OF COELIAC DISEASE **AE Muller**, MT Donnelly, CML Smith, MJ Grundman, GKT Holmes, PJ Toghill. Depts of Medicine, University & City Hospitals, Nottingham; Dept of Neuropathology, Royal Hallamshire Hospital, Sheffield; Derbyshire Royal Infirmary and Chesterfield & North Derbyshire Royal Hospital.

Cooke & Smith in 1966 highlighted the neurological complications of coeliac disease (CD). Of their 16 cases, 9 died from progressive neuromyopathy. The aetiology is unknown but patients (pts) refractory to a gluten free diet (GFD) may be more susceptible. No nutritional cause has been identified, but some cases of cerebellar disease have been associated with vitamin E deficiency.

We present 4 pts, 1 female (pt 1, 32yr) and 3 males aged 7, 58 & 63 years (pts 2-4) at onset of the neurological complications of CD. All had subtotal villous atrophy, which in 3, showed no improvement with a strict GFD. None had lymphoma. 2 pts were on both folic acid and vitamin B₁₂ replacement. Comprehensive trace element and vitamin studies were normal in each pt, except pt 2 with a low vitamin E level. There was no response to treatment with vitamin E in this pt.

Pt 1 died of a rapidly progressive sensorimotor neuropathy within 6 months of the diagnosis of CD. Neuropathological examination revealed capillary hyperplasia throughout the cerebral white matter and a diffuse inflammatory cell infiltrate, with neuronal loss in the cerebellar but not cerebral cortex. Nerve roots showed combined demyelination and axonal degeneration and a muscle biopsy showed neurogenic atrophy.

Pts 2-4 were disabled from a combination of dorsal column and cerebellar disease. In pt 2, the neurological problems antedated the diagnosis of CD. Pt 3 had a non-progressive peripheral neuropathy and ataxia for 20 yrs. A brain CT scan in pt 4 showed cerebral & cerebellar atrophy. This pts disease was complicated by mesenteric lymph node cavitation.

Neurological complications are a recognised but unusual manifestation of CD which may be rapidly fatal. Pts whose small bowel histology fails to improve on a GFD may be at increased risk. Symptoms may precede the diagnosis of CD. There is no recognised nutritional deficiency. The central and peripheral nervous system inflammatory infiltrate in pt 1 favours an immune mediated disorder.

W14

LARGE SCALE POPULATION SURVEY OF ANTIBODIES TO GLIADIN, RETICULIN AND ENDOMYSIUM.

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Coeliac disease is often under diagnosed, particularly in cases which are atypical or asymptomatic. This study is the first step in the comprehensive assessment of the prevalence and clinical profile of the adult condition in our community.

Blood samples from 5 large representative population surveys: MONICA 1, 2 and 3 (1983, '86, '91), CINDI (1986) and Change of Heart (1988) were tested for IgA anti gliadin antibody (AGA) by ELISA, anti reticulin antibody (ARA) and anti endomysial antibody (EMA) by indirect immunofluorescence. Samples were tested from 5885 subjects in the age range 12 - 64, with equal numbers of males and females and similar numbers at each age point.

The frequency distribution of AGA titres was heavily skewed to the left with a long tail on the right and the 95th centile at 98AU (arbitrary units). Using 100 AU for AGA as the conventional level for a positive result the numbers of subjects with positive antibodies were:

Ig A anti gliadin antibody (AGA)	316 (5.4%)
Ig A anti reticulin antibody (ARA)	34 (0.6%)
Ig A anti endomysial antibody (EMA)	38 (1.1%)

The prevalence of AGA was equal in males and females, and increased with age from 12 to 65: in the age group 46-65 it was more than twice that in those under 25 (6.2% vs 2.5%). In the Monica series of surveys which were carried out in the same geographical area at 3 time points in 8 years, there was no significant change in the prevalence of positive antibody serology.

The predictive value of these tests for coeliac disease, individually or in combination, when used in the context of these surveys is unknown but they suggest that the prevalence of the condition may be considerably higher than the presently accepted figure of 1:1500 (0.07%) in Northern Ireland. The similarity of antibody prevalence at 3 time points suggests stability of disease prevalence which is in contrast to the observed apparent clinical increase in adult coeliac disease. The next aim of our study is the clinical follow-up of subjects to clarify these issues. MONICA = Multinational MONitoring of trends and determinants in Cardiovascular disease
CINDI = Countrywide Integrated Non-communicable Disease

W16

PREVALENCE, DEGREE AND PATHOPHYSIOLOGY OF BONE LOSS IN ADULT COELIAC DISEASE (CD). **Corazza G.R.**, Di Sario A., Cecchetti L., Tarozzi C., Jorizzo R., Gasbarrini G. I Department of Medical Pathology, University of Bologna and Division of Nuclear Medicine, Maggiore Hospital, Bologna, Italy.

Seventeen untreated coeliacs, 14 coeliacs on a gluten-free diet (GFD) and 24 age- and sex-matched healthy volunteers (HV) were studied. In each subject, bone mineral density (BMD) and several parameters of bone metabolism were measured. BMD, expressed as Z-score, was lower in untreated (-2.0 ± 0.9 SD) and treated CD (-1.5 ± 0.6) than in HV (0.1 ± 0.6 ; $p<0.00001$ and $p<0.0001$, respectively), and higher ($p<0.05$) in treated than in untreated CD. All but one untreated coeliacs had a low BMD. Serum calcium was lower both in untreated (2.0 ± 0.2 mmol/L) and treated CD (2.3 ± 0.1) than in HV (2.4 ± 0.1 ; $p<0.0001$ and $p<0.02$, respectively), and higher ($p<0.0005$) in treated than in untreated CD. iPTH was higher ($p<0.05$) in untreated (67.9 ± 70.0 ng/mL) than in treated CD (27.8 ± 16.6) and HV (25.5 ± 11.3). 25-vitamin D was lower in untreated than in treated CD and HV, whereas 1,25-vitamin D was higher in untreated and treated CD than in HV, and lower in treated than in untreated CD. All indices of bone remodelling (osteocalcin, propeptide of type I procollagen and telopeptide of type I collagen) were higher in untreated than in treated CD and in HV, and positively correlated, in untreated CD, with serum iPTH. Our results show that a significant degree of bone loss in almost invariably present in untreated CD, and that GFD is able to improve but not to restore bone mass to normal. The high serum levels of 1,25-vitamin D found in untreated CD could be the consequence of hypocalcaemia and of the increased renal conversion, iPTH mediated, of 25- to 1,25-vitamin D; the persistence of high levels of the latter metabolite after treatment could be due to the incomplete normalization of calcium balance after GFD. Moreover, our results show that untreated CD is characterized by an increased bone turnover which increases bone loss and which is caused and maintained by a secondary rise in serum iPTH.

W17

FRACTIONAL CALCIUM ABSORPTION AND BONE MINERAL DENSITY IN COELIAC DISEASE. Butcher GP, Pazianas M, Ang L, Zaidi M, Maxwell JD. St George's Hospital Medical School, London SW17 0RE, U.K.

The cause of osteopenia in coeliac disease is unknown. Reduced absorption of dietary calcium despite adherence to a gluten free diet may be one mechanism. To study this, bone mineral density (BMD) and fractional calcium absorption were determined in female coeliac disease patients. BMD was determined by dual energy X ray absorptiometry (DEXA). Fractional calcium absorption was measured by employing a single isotope (⁴⁵Ca) method. A meal of 150 ml soya milk with 0.6 MBq of ⁴⁵Ca added, two slices of gluten-free toast and corn flakes, containing approximately 200 mg calcium in total, was given following an overnight fast. Blood was drawn at 0 and 5 hours and ⁴⁵Ca concentration determined by liquid scintillation counting (⁴⁵Ca is a pure β emitter). Empirical measures of isotope content were obtained by correcting for serum calcium, height and weight (after Heaney, 1985).

Seventeen women were studied (median age, 47 years; range, 24 to 73 years), with a median time since diagnosis of 4 years (range, 1 - 12 years). Whole body BMD (expressed as Z scores, i.e. variations from the mean by standard deviations, SD) was reduced when compared with controls matched for age, sex and ethnicity (mean Z score, - 0.33). Five of the seventeen subjects studied had a BMD which was >1 SD below the mean. Whole body calcium content was 862 g (range, 482 - 1191). Mean fractional calcium absorption was 37% (range, 17 - 53). Fractional calcium absorption did not correlate with BMD determined at three sites, serum calcium, whole body calcium, age or duration of treatment.

In conclusion, we confirm an increased incidence of osteopenia in treated coeliac disease patients and conclude that osteopenia or whole body calcium in these patients is not solely determined by calcium absorption.

W19

AN ENDOLUMINAL BRUSH TO DETECT THE INFECTED CENTRAL VENOUS CATHETER IN SITU IN PATIENTS RECEIVING INTRAVENOUS NUTRITION (IVN). M.J.TIGHE, P.KITE*, M.J.McMAHON.

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Catheter-related sepsis, (CRS), is a potentially life-threatening complication in patients receiving IVN. Suspicion of CRS usually leads to removal of the catheter. However, 80% of removed catheters are found to be sterile after removal. A prospective study was performed on 60 patients receiving IVN, to compare the diagnosis of CRS by a newly-developed endoluminal brush, which slides along the catheter lumen and picks up fibrin, with the removed catheter tip. Quantitative blood cultures (QBC) and entry-site skin cultures (ESC) were also performed. Results of endoluminal brush culture (EBC) were compared with standard catheter tip culture, QBC and ESC in 60 catheters. A positive result was indicated by the culture of >15 colony forming units at 48 hours.

Results:

Tip culture	EBC		QBC		ESC	
	+ve	-ve	+ve	-ve	+ve	-ve
+ve = 17	14	3	5	12	7	10
-ve = 43	2	41	0	43	1	42

The sensitivity and specificity of the brush compared with tip culture was 0.82 and 0.95, with a positive predictive value of 0.87. QBC and ESC were specific (1.0 and 0.98), but sensitivity was low (0.29 and 0.41). Correlation with tip culture was significantly better with the brush than QBC (p<0.01) or ESC (p<0.02).

Conclusion: Endoluminal brush culture detects central venous catheter infection accurately, without the need for catheter removal.

W18

EFFECT OF A GLUTEN FREE DIET ON BONE DENSITY IN COELIAC DISEASE X McFarlane, A K Bhalla, D A F Robertson. Royal United Hospital, Combe Park, Bath BA1 3NG.

Osteopaenia (low bone mineral density) is common in patients with newly diagnosed adult coeliac disease. The aim of this study was to determine whether treatment with gluten free diet (GFD) is associated with an improvement in bone mineral density (BMD) .

METHODS: 20 patients (13 female, 7 male, average age 49.6 years) with newly diagnosed coeliac disease had BMD measured at the lumbar spine (L1 - 4) and femoral neck on entry to the study and a repeat scan after one year of GFD. BMD was measured using an Hologic QDR 1000 X-ray bone densitometer and was expressed as a Z score, that is the number of standard deviations by which a patients BMD differs from the mean of age and sex matched normals.

RESULTS: 9 patients (45%) had mild ($-2 \leq Z < -1$) and 8 patients (40%) had severe osteopaenia ($Z < -2$). Repeat densitometry demonstrated significant improvement in BMD at lumbar spine and femoral neck (p<0.02, Wilcoxon signed rank test). Bone biopsy, performed on 4 of the most severely osteopaenic patients, demonstrated frank osteomalacia in the 2 patients who had presented with bone pain. 2 other patients had severe osteoporosis.

	Mean initial Z score	Mean change in Z score/year	% change in BMD /year
Lumbar spine	-1.46	+0.47	+4.50
Femoral neck	-1.39	+0.30	+4.51

COMMENT : Osteoporosis is common and frequently severe in newly diagnosed patients with adult coeliac disease, but no symptoms of bone pathology. Clinical, biochemical and histological evidence of osteomalacia was found in 10% of patients with newly diagnosed coeliac disease. The large improvement in BMD with gluten free diet in both osteomalacia and osteoporosis demonstrates the potential for improvement of these abnormalities and underlines the importance of the gluten free diet in all patients with coeliac disease.

W20

Haemodynamic and neuroendocrine responses to feeding: relationship to energy content of a meal.

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Introduction. We have previously demonstrated a significant relationship between energy content of a meal and superior mesenteric artery blood flow. Here we describe the haemodynamic and neuroendocrine responses to meals of varying energy content.

Method. Six healthy volunteers aged between 22 and 39 years were examined supine and after an overnight fast on four separate occasions. Blood pressure and pulse rate were measured by automated sphygmomanometer. Plasma noradrenaline (NA) concentrations of arterialised venous blood were also measured. Readings were taken at rest and at intervals for 120 minutes after ingesting an isovolumetric meal (300ml) of varying energy content based on the Lundh meal. In a randomised, blinded procedure, the volunteers received drinks containing 800 (meal 1), 1600 (meal 2), 2400 (meal 3) and 4800 (meal 4) kJ.

Results. (Expressed as mean[SEM] and compared using Student's t-test). Pulse rate, systolic blood pressure and mean arterial pressure all increased and diastolic pressure decreased over the 120 minutes after each meal. The size of the overall increase from baseline of pulse rate (calculated using trapezoid method for estimating area under curves) was related to meal energy content, increasing from 1.85[6.05] beats/min for meal 1 to 5.46[7.1] beats/min for meal 4 (r = 0.9919; p = 0.008). Other changes were not significant (n/s). NA concentration increased after each meal. Meal 1 produced a peak increase from 124.8[26.49] to 170.6[40.9] ng/l (n/s); meal 2 from 115.6[13.95] to 200[45.17] ng/l (n/s); meal 3 from 119.6[211.5] to 200.0[36.2] ng/l (p = 0.03); meal 4 from 122.6[16.18] to 177.3[17.68] ng/l (p = 0.02). The overall increase (area under curves) in NA concentration also appeared to be related to energy content, increasing from 14.5 ng/l after meal 1 to 33.9 ng/l after meal 4 (r = 0.9019; p = 0.036).

Conclusions. Post-prandial pulse rate and sympathetic nervous system activity in healthy young adults appear to be related to the energy content of a meal.

W21

A RANDOMISED COMPARISON OF PERCUTANEOUS ENDOSCOPIC GASTROSTOMY FEEDING AND NASOGASTRIC TUBE FEEDING FOLLOWING ACUTE DYSPHAGIC STROKE.

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Most patients admitted with acute neurological dysphagia are fed via a nasogastric (NG) tube. Percutaneous endoscopic gastrostomy (PEG) feeding is a well established alternative which has many potential advantages. The aim of this study was to identify whether early insertion of PEG after acute dysphagic stroke is of greater benefit to patients.

Methods: 20 patients (12 female, mean age 80 years) were randomised at 2 weeks to receive nutritional support via NG tube or PEG. Patients were monitored by weight, anthropometric measurements and blood indices. Patients were followed prospectively and treatment assessed on the basis of changes in the above indices together with mortality, length of hospital stay, and treatment failure rates.

Results: 12 patients (6 female, mean age 79) received PEG feeding and 8 (6 female, mean age 80) received NG feeding. Survival at 6 weeks was significantly higher in the PEG group with 1 death (8%) compared to 4 deaths (50%) in the NG group ($p < 0.05$). NG tubes were pulled out and resited in 6 patients (mean, 4 NG tubes per patient, range 1 - 10) compared to no tube replacements in the PEG group ($P < 0.01$). 5 patients from the PEG group were discharged within 6 weeks of the procedure compared to 1 patient from the NG group. Those in the PEG group had fewer treatment failures (0 versus 3) and showed a greater improvement in nutritional status at 6 weeks compared to the NG fed group.

This study suggests that early PEG feeding is superior to NG feeding in patients following acute dysphagic stroke.

W23

A COMPARISON OF THREE-DIMENSIONAL AND CONVENTIONAL MANOMETRIC METHODS IN ASSESSING CHANGES IN LOWER OESOPHAGEAL SPHINCTER PRESSURE DURING FASTING

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Manometric recordings of lower oesophageal sphincter (LOS) pressure show the LOS to be a dynamic structure with variations in measured pressure over time. Falls in LOS pressure have been equated with gastro-oesophageal reflux events. Observations on the LOS have traditionally been made with solitary side hole manometry or with a sleeve device. A more accurate assessment may possibly be made by taking into account the sum of pressures acting along the length and around the circumference of the sphincter.

Ten healthy volunteers (6M, age 24-49) were fasted for 4 hours after which a four channel, water-perfused catheter was passed via the nose, through the LOS and into the stomach. Using a station pull-through technique, LOS pressure was recorded at 10mm intervals along the length of the LOS using external pressure transducers. Four radial pressures were recorded at each station and a three-dimensional LOS pressure vector volume was calculated from the formula:

$$0.5[(P_1 + P_3)(P_2 + P_4)] \times \text{distance between stations.}$$

This was compared to maximum sphincter pressure defined as the average of the maximum pressure from each channel. Recordings were made every 15 minutes for two hours.

There was no significant difference between the ranges of LOS pressure vector volumes throughout the monitoring period. However, the range of results when recording "maximum" sphincter pressure varied significantly over time. Only at times 30, 45, 105 and 120 minutes did sphincter pressure show no significant difference from the initial pull through results (Wilcoxon sign rank test).

This study conflicts with earlier reports of variation in sphincter pressure over time. Although individual points in the LOS change their pressure during fasting, the three-dimensional integration of these pressures remains relatively constant. Despite changing "shape" the competence of the LOS stays the same.

Oesophagus W22-W32

W22

CEREBRAL EVOKED POTENTIALS. ARE THEY USEFUL IN ASSESSING OESOPHAGEAL MOTILITY DISORDERS.

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Introduction: Cerebral evoked potentials (CEP) following electrical stimulation (ES) of the oesophagus can be detected by scalp electrodes. Their clinical usefulness is uncertain. **Aim:** To assess the relevance of this technique in documenting the pathophysiology of oesophageal motility disorders. **Method:** ES by electrodes on a PVC catheter was performed in the proximal and distal oesophagus in 10 volunteers and 13 patients with oesophageal motility disorders (one diffuse oesophageal spasm [DOS], one nutcracker oesophagus, eight non-specific motility disorder [NSMD] and three idiopathic achalasia) diagnosed by oesophageal manometry. The stimulus intensity in milliamperes was increased until definite sensation occurred and at this intensity 50 repetitions at frequency 0.2Hz were performed and averaged. Detection of the ECG signal via the catheter was monitored to ensure good electrode to mucosa contact. **Results:** A multiphasic CEP was recorded with upward (N1, N2 etc) and downward deflections (P1, P2 etc) in all volunteers. 5 patients with NSMD had normal CEP. There was total sensory denervation, ie no sensation or CEP, in all three patients with achalasia. Two patients (DOS and 1 NSMD) had normal sensation but absent early deflections, N1 and P1, (selective neuropathy). 1 patient with NSMD had normal sensation but delayed N1, P1 deflections (neuropathy with delayed nerve conduction). 2 patients (1 NSMD and nutcracker) had a low sensory threshold with normal CEP (hypersensitivity) **Conclusion:** Oesophageal motility disorders are associated with a variety of abnormalities in oesophageal afferent innervation. The use of CEP may assist rational classification of these disorders.

W24

UNDERSTANDING THE PATHO-PHYSIOLOGY OF GASTRO-OESOPHAGEAL REFLUX (GOR) USING A NEW DYNAMIC MODEL **SS Kadirkamanathan, JG Laufer, DF Evans, CP Swain.** Gastrointestinal Science Research Unit, The London Hospital Medical College, London

Patients often experience GOR after eating or during exercise when intragastric and intra-abdominal pressures are raised. Yet the importance of these pressure fluctuations and that seen during normal respiration have not been addressed with mechanical models previously developed to investigate the mechanics of GOR and lower oesophageal sphincter (LOS) function. We have developed a new, four compartment mechanical model which has been used to study the complex pressure effects on GOR in vitro.

Rubber tubing was used to construct the oesophagus, stomach and LOS which were placed inside a two chamber perspex container representing the thorax and abdomen. LOS position in relation to the two compartments, LOS length and pressure (LOSP) could be altered. Intra-abdominal and intra-thoracic pressures (IAP & ITP) could also be varied rhythmically to simulate breathing and exercise. Intragastric pressure (IGP) was varied with a column of water at different heights. Pressure changes were measured with transducers and plotted on a chart recorder. Reflux was measured as the flow of water through the LOS (ml/min) in static and dynamic situations (respiration and exercise) varying LOS length, LOSP, IGP, IAP and ITP.

RESULTS: Static experiments of LOS competence were in agreement with published literature and confirmed the validity of the model. Respiratory and exercise simulation (IAP=15-40mmHg) at given LOSP (5-40mmHg), LOS length (1-3cm) and IGP (5-45mmHg) caused significant increase in GOR ($p=0.006$ & 0.027 respectively) when compared with the same values in the static state. An increase of IGP (simulating post-prandial gastric distention), caused even greater reflux when compared with the same range of IAP during the exercise simulation ($p=0.007$). At sphincter length 1-2 cm, more reflux occurred when the sphincter was in the thorax, but a 3 cm sphincter was competent irrespective of its position.

CONCLUSION: Our model has demonstrated the dynamics of GOR in relation to pressure differences across the cardia and has shown that GOR is greater during respiration and exercise simulation. It has also shown that the most important factor in refluxogenesis is raised intragastric pressure. The model has illustrated that a long thoracic sphincter can be competent. It may also be useful in the evaluation of anti-reflux compounds that rely on barrier effect to prevent reflux.

W25

MOTOR ACTIVITY OF THE OESOPHAGUS PROBABLY ONLY HAS A MINIMAL EFFECT ON ACID CLEARANCE
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Acid clearance after gastro-oesophageal reflux (GOR) depends on clearance by oesophageal peristalsis and neutralisation by saliva. The last motor activity during GOR demonstrates the greatest acid clearance (Ref). This study investigated the correlation between acid clearance (as defined by oesophageal pH) and particular parameters of the last oesophageal motor activity. Oesophageal pressures and pH were recorded (Gaeltec) over 24-hours on 17 patients with GOR. Pressures were measured at 15, 10 and 5 cm above the lower oesophageal sphincter (LOS). Oesophageal pH was monitored at a level 5 cm above the LOS. Manometric activities were classified as either peristaltic (P) or non-peristaltic (NP). 431 reflux episodes (pH<4) with the 86 associated NP and 345 associated P activities during the last clearance were analyzed. The medians of the pH increments for each patient's associated NP and P were compared, no significant difference was found (p>0.05). Correlation between patient's pH increments and the associated P parameters of the last clearance were as follows: (A15, A10, A5, D15, D10 and D5 are the amplitudes and durations of the P contraction at 15, 10 and 5cm above the LOS respectively; V is the velocity of the P wave travels from A15 to A5).

pH increments versus	Mean Correlation(range)	p-value
A15 (mmHg)	-0.02 (-0.57,0.58)	0.78
A10 (mmHg)	-0.02 (-0.54,0.49)	0.83
A5 (mmHg)	-0.05 (-0.69,0.60)	0.52
D15 (sec)	-0.01 (-0.59,0.61)	0.87
D10 (sec)	0.05 (-0.53,0.63)	0.60
D5 (sec)	-0.03 (-0.61,0.43)	0.69
V (cm/sec)	-0.02 (-0.87,0.40)	0.84

Conclusion: No association was found between the pH increments and the P amplitude, duration or velocity or whether it was P or NP during the last acid clearance of GOR.

Ref: Anggiansah et al (1993) Gut 34 (Supp 4): F256

W27

THE RELATIONSHIP BETWEEN GASTRO-OESOPHAGEAL REFLUX AND PALATAL DENTAL EROSION. DW Bartlett, DF Evans*, A Anggiansah*, W Owen* and BGN Smith. Depts of Conservative Dental Surgery & *Surgery UMDS and *Gastrointestinal Science Research Unit, London Hospital Medical College, London.

Severe palatal dental erosion is a common problem in dentistry often requiring significant time and money to restore the function and appearance of the teeth. Palatal dental erosion has been associated with anorexia and bulimia nervosa, chronic alcoholism and gastro-oesophageal reflux (GOR) disease. The aim of this study was to investigate GOR in patients attending Guy's Dental Hospital with evidence of palatal dental erosion. Twenty six subjects (age range 15-74), 15 with occasional reflux symptoms, were investigated for a minimum of 18 hours, including the night. The severity of dental erosion in each patient was assessed clinically by a standard tooth wear index (TWI). Distal and proximal pH was monitored using a dual channel antimony electrode positioned at 5cm and 20cm above the lower oesophageal sphincter, determined by manometry. Oral pH was monitored simultaneously using a pH-sensitive radio-telemetric capsule held palatally in a soft acrylic appliance. Signals were detected by a headband aerial and all pH data were logged on two portable ambulatory recorders. GOR was analysed for % time <pH4 in the distal oesophagus and <pH4 and 5 in the proximal oesophagus. Oral pH was analysed for the % time <pH5.5 and 6 (pH5.5 & 6 are possible thresholds for tooth demineralisation). Eighteen patients (70%) were diagnosed as having pathological GOR by distal oesophageal pH criteria. The mean % times were 7.8 (SD=7.9) <pH4 in the distal oesophagus, 2.2 (3.6) <pH4 & 5.3 (7.4) <pH5 in the proximal oesophagus and 11.4% (24.1) <pH5.5 orally. The number of combined reflux episodes in the proximal oesophagus and mouth was related to the % time <pH4 in the distal oesophagus (p=0.006). There was also a relationship between the longest time <pH5 in the proximal oesophagus and longest time <5.5 (p=0.06) & <6 (p=0.05) in the mouth in the upright position and <5.5 (p=0.03) in the supine position. Oral pH was also related to the amount of erosion measured by the TWI (<pH5.5 p=0.01 and <pH6 p=0.02). Our results showed that patients presenting with palatal dental erosion were more likely to suffer from pathological GOR and this was related to oral reflux and the amount of tooth erosion. Palatal dental erosion is therefore an important clinical sign for GOR disease and should be used diagnostically by both dentists and gastroenterologists.

W26

THE NATURAL HISTORY OF REFLUX OESOPHAGITIS AND ITS EFFECT ON QUALITY OF LIFE: A 10 YEAR FOLLOW-UP. McDougall NI¹, Johnston BT², Kee F¹, Collins JSA², McFarland RJ³, Watson RGP¹, Love AHG¹. Dept of Medicine, Queen's University Belfast¹, Royal Victoria Hospital, Belfast², and Ulster Hospital Dundonald³, UK.

Aims: To assess parameters of quality of life and the level of reflux symptoms in patients previously diagnosed as having oesophagitis.

Methods: One hundred and twelve patients in whom grade I-III oesophagitis (modified Savary-Miller) was diagnosed 10 to 12 years ago were traced and invited to complete a detailed symptomatic questionnaire incorporating the Short Form-36 (SF-36) general health survey questionnaire. Results were compared with SF-36 data for a sample (n=3015) of the overall Northern Ireland (N.I.) population (provided by the Department of Public Health Medicine, Eastern Health and Social Services Board (N.I.)).

Results: Fourteen patients were deceased (none due to oesophageal disease), 28 failed to respond and 70 replied (33 male, mean age 58 yrs, range 28-81) with mean follow-up period of 11 years (121-153 months). Twenty-five patients (36%) still reported daily heartburn. Two patients (2.9%) had developed oesophageal strictures and another patient had undergone anti-reflux surgery. Patients were divided into those with (n=32) and those without (n=38) major medical problems other than reflux disease. The table shows the quality of life scores in these 2 groups along with the overall group and the N.I. population sample.

	Physical Function	Role - Physical	Bodily Pain	Gen. vitality	Social Health	Role - Emotion	Mental Health
N.I. pop.	79.7	76.2	73.1	69.0	59.6	83.3	79.9
Overall	60.4*	55.0	59.8	58.4	51.4	60.9*	74.7
With prob.	45.5*	28.9*	48.7*	50.6*	43.1*	52.5*	63.5
Without	72.9	77.0	69.2	64.9	58.3	67.9*	84.1

*P<0.05 using Multiple Linear Regression

Even after allowing for other medical problems, patients in the heartburn only group still had a significantly lower score for social function.

Conclusion: Patients previously diagnosed as having oesophagitis have significantly lower scores for some quality of life parameters 10 years after initial diagnosis, and 36% still have heartburn at least daily.

W28

ERADICATION OF HIGH GRADE DYSPLASIA IN COLUMNAR LINED (BARRETT'S) OESOPHAGUS BY PHOTODYNAMIC THERAPY WITH ORAL 5-AMINOLAEVULINIC ACID AND 630NM LIGHT. H.Barr, T Dix, D.Roberts, N Shephard, Departments of Surgery, Physics and Pathology, Gloucester Royal Hospital, Great Western Road, Gloucester, GL1 3NN.

Photodynamic therapy(PDT) involves the administration of a photosensitiser and subsequent activation in tissue by light to produce a local cytotoxic reaction. Most treatment involves the administration of exogenous photosensitiser which leads to non-specific tumour accumulation in stroma and not the neoplastic cell with prolonged general photosensitivity. The administration of oral 5-aminolaevulinic acid (5-ALA), a precursor of haem induces intracellular accumulation of the photosensitiser protoporphyrin IX (PpIX). The accumulation of PpIX after oral 5-ALA (60 mgkg⁻¹), was measured in dysplastic columnar lined oesophagus, oesophageal adenocarcinoma arising in columnar lined oesophagus, normal gastric and oesophageal tissue using quantitative fluorescence photometry (biopsy of 8 patients). Selective accumulation of PpIX occurred in dysplastic columnar lined oesophagus (x3) and adenocarcinoma (x6) after four hours. Six patients with high grade dysplasia in columnar lined oesophagus were treated with photodynamic therapy (laser light delivered with a 3cm cylindrical diffusing fibre at 630nm) after oral administration of 5-ALA(60mgkg⁻¹). Three patients had macroscopic adenocarcinoma. All patients were treated at endoscopy under sedation with an energy fluence of 90-150 Jcm⁻². All patients received 40 mg omeprazole daily. Follow-up endoscopy and multiple biopsy at 1-2 monthly intervals, for 2-18 months, demonstrated squamous regeneration in the dysplastic columnar lined oesophagus in four patients with regeneration over metaplastic tissue in two patients. A small area of low-grade dysplasia remained in one patient and was destroyed with thermal laser photoablation. No effect (including measurement with endoscopic ultrasound) was seen in the eradication of adenocarcinoma. Endogenous photodynamic therapy with 5-ALA combined with long term omeprazole can eradicate superficial high grade dysplastic columnar lined oesophagus, but is ineffective in destroying macroscopic carcinoma.

W29

ENDOLUMINAL ULTRASOUND : ACCURACY AND LIMITATIONS IN LYMPH NODE EVALUATION FOR OESOPHAGEAL CARCINOMA

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Metastasis to regional lymph nodes is an important prognostic factor in oesophageal cancer. Endoluminal ultrasound (EUS) is highly accurate in determining local tumour stage, but evaluation of regional lymph nodes may be less reliable.

We performed preoperative lymph node evaluation using EUS in 30 patients with primary oesophageal cancer. A total lymph node count was performed and each node detected was designated benign or malignant according to its size, shape, echo density and homogeneity. Each patient subsequently underwent oesophagectomy and the histological lymph node findings were compared with EUS. (Table) Ten patients had complete oesophageal obstruction which prevented assessment distal to the tumour.

	Total nodes	Malig. nodes	Benign nodes	Mal:Ben ratio
Histology (n=30)	262	74 (28%)	188(72%)	1 : 2.6
EUS-all cases (n=30)	126	78 (62%)	48 (38%)	1 : 0.6
EUS-patent lumen (n=20)	83	48 (58%)	35 (42%)	1 : 0.7

EUS correctly predicted the lymph node stage (N0 or N1) using the TNM staging system in 25 (81%) of the patients. Understaging occurred once and overstaging four times. EUS actually detected only 48% of the total nodes found on histological examination of the resected specimens. The data suggest that EUS reliably identified malignant nodes, whereas most of the nodes that it failed to detect were benign. Oesophageal obstruction did not affect the proportions of malignant and benign nodes that EUS detected.

Although EUS does not identify every regional lymph node it does reliably detect most lymph node metastases. Its failure to image every benign node is less significant, and does not detract from the usefulness of EUS for lymph node staging.

W31

AGGRESSIVE SURGERY FOR OESOPHAGEAL CARCINOMA - IS IT WORTH IT ?

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Surgery offers the best palliation and the only hope of cure for the majority of patients with oesophageal carcinoma. Over a 5-year period 436 patients underwent operation. Dysphagia was the commonest presentation (82%). 92 patients proved irresectable. 344 were resected via left thoraco-laparotomy (96%) or a transhiatal approach. Alimentary continuity was restored with gastric tube (338), Roux loop (4) or colon (2). Proximal third tumours accounted for 3% of cases, mid third for 23% and distal third and OG junction for 74%. 40% of patients were over 70 years and there were 18 octogenarians. Significant cardio-respiratory disease was present in 110 (32%).

30-day mortality was 5.5% (19/344). 20 patients (6%) required early re-operation (8 bleeding, 7 chylothorax, 5 anastomotic leaks). Significant complications occurred in 34% of patients. These included anastomotic leak (6.7%), chylothorax (4%), IPPV (8.7%), tracheostomy (10%), TPN (10%), renal failure (2%). Median in-patient stay was 13 days (7-103).

All 312 survivors were able to swallow on discharge from hospital. 110 required dilatation mainly for benign anastomotic stricture. Overall survival at one, three and five years was 49%,18% and 8%. Sub-group analysis revealed better survival in patients with squamous carcinomas (53%, 22%, 10% at 1, 3 and 5 years respectively) and dismal outcome in lymph node positive adenocarcinomas (40%, 7%, 1% at 1, 3 and 5 years).

Conclusion: Resection may be performed safely in a relatively elderly population and achieves good palliation of dysphagia . Poor survival in patients with adenocarcinoma reflects locally advanced disease. However significant medium-term survival can be achieved in those with localised adenocarcinoma and squamous tumours.

W30

QUALITY OF LIFE IN PATIENTS WITH OESOPHAGEAL CANCER
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Quality of life (QOL) analysis may aid decision making in the management of patients with oesophageal cancer but must be clinically valid to be useful. This study determined if the European Organisation for Research and Treatment of Cancer quality of life core questionnaire (Aaronson 1993) demonstrated differing results in two clinically distinct groups of patients with oesophageal cancer and examined how a dysphagia score relates to QOL.

Forty-five patients, 24 post oesophagectomy, (median follow up 17 weeks) and 21 who had received purely palliative treatment, (median follow up 10 weeks), completed the questionnaire. Dysphagia was graded on a 1 to 4 scale. Dysphagia grade and QOL scales were linearly transformed such that results ranged from 0 to 100.

Patients treated by oesophagectomy (median age 64 years), reported good emotional and physical functioning and relatively low symptom burdens. The palliative treatment group (median age 72 years), reported significantly worse emotional and physical function, and more symptoms. Dysphagia grade was worse in the palliative treatment group.

This questionnaire differentiated between the subgroups of patients with oesophageal cancer. Dysphagia grade is one indicator of QOL, the disease and treatment effects other important QOL issues.

Functional scales*	Oesophagectomy Median score	Palliative gp Median score	p value ¹
Emotional function	87	59	0.025
Physical function	60	40	0.011
Symptom scales**			
Fatigue	39	67	0.096
Nausea	16	50	0.070
Appetite loss	33	66	0.012
Pain	0	33	0.001
Dysphagia grade	33	66	0.022

* High score = better functioning ** High score = worse symptoms
¹Mann Whitney U test

W32

PALLIATION OF OESOPHAGEAL CARCINOMA WITH EXPANDABLE METAL PROSTHESES IS A COST-EFFECTIVE PROCEDURE.

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Introduction: Oesophageal carcinoma can be palliated by endoscopic procedures and intubation. Recently the use of expandable metal prostheses (EMP) has become available but cost limits their use. **Aim:** To compare the use of standard palliative methods with EMP with respect to the quality of palliation and hospital costs. **Method:** 27 patients with carcinoma of the oesophagus receiving standard palliative treatment (S) were compared to twelve patients receiving EMP in the period April 1992 to May 1994. The number of palliative procedures, days spent as an hospital in-patient and the best dysphagia score produced during palliation were recorded. (Dysphagia score ranging from 0 = no dysphagia, 1 = difficulty with particular foods only, 2 = semi-solid diet only, 3 = liquids only, 4 = dysphagia to all liquids and saliva). Results expressed as median(range) and statistical analysis using Mann-Whitney. **Results:** Total days as in-patient, S = 25.93(1-68), EMP = 6(2-14), p = 0.0004. Number of palliative procedures, S = 3(1-9), EMP = 1(1-2), p = 0.0011. Best dysphagia produced by palliation S = 3(0-3), EMP = 1(0-2), p = 0.0001. **Conclusion:** Palliation of oesophageal carcinoma with EMP produces good palliation of dysphagia. Fewer procedures are required and the number of in patient days is reduced with EMP. This considerably reduces hospital costs. EMP is cost effective.

Liver W33-W43

W33

REGULATION OF PORTAL VENOUS PRESSURE BY INTRAHEPATIC SHUNTS AFTER MICROSPHERE INJECTION IN THE RAT
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Previous rat models of portal hypertension using intraportal injection of microspheres (1) generated a portal venous pressure of only 50% above basal values. This study used larger numbers of microspheres and generated greater increases in PVP following sequential injections of 15µm (Group 1) and 80µm (Group 2) diameter microspheres respectively, after steady-state conditions for 20 minutes. Sequential injections of different sized microspheres in ascending order (15+40+80µm; Group 3) or descending order of diameter (80+40+15µm; Group 4) did not generate further increases in PVP. We confirmed the presence of intrahepatic shunts in the normal rat liver by 3 observations; 1) although the PVP was raised further by increasing the number of microspheres injected, the much higher value (36.6-43.2 mmHg) measured during total portal vein occlusion could not be attained; 2) the wedged hepatic venous pressure (WHVP) which always decreased during portal venous occlusion, showed a significant increase following the sequential injection of 15µm spheres (Group 1); and 3) numerous microspheres were located in the pulmonary vascular bed. It is suggested that the maximum PVP obtained by portal venous occlusion is unattainable in the normal liver by intraportal injection of microspheres due to the presence of patent intrahepatic portal-systemic shunts.

Group	PVP			%increase	WHVP	
	Basal	After	After-basal		Basal	After
1	7.4±1.6	14.9±3.6 *	7.5±2.8 *	102.2±35.6 *	7.0±1.0	12.4±1.8†
2	6.7±1.4	24.0±2.2 *	17.3±2.7 *	272.3±78.0 *	6.7±0.7	3.0±0.6†
3	7.7±0.8	19.9±3.7	12.3±3.9	162.8±60.1	-----	-----
4	7.4±1.0	20.3±1.0	12.9±1.5	178.6±41.0	-----	-----
control	7.8±0.5	no change	no change	no change	6.7±0.8	no change

*P<0.05 vs other groups, Student's unpaired t-test, †P<0.01 vs basal, Student's paired t-test. Results shown are mean ± standard deviation, n=6 per group.
1) Jaffe V., Alexander B., Mathie RT. (1994) Gut 35: 815-818.

W34

Reduction in renal blood flow with acute increase in the portal pressure gradient. Evidence for the existence of hepatorenal reflex in man? Dept Med, R.I. Edin Jalan, R., Forrest, E.H., Redhead, D.N, Hayes, P.C.

Hepatorenal reflex has been demonstrated in rats by induction of acute portal hypertension. The aim of this study was to investigate the mechanism of this reflex in man.

Material and Methods: Ten patients (M:F=6:4, mean age 53 (3.5)) with underlying cirrhosis (due to alcohol 9 and primary biliary cirrhosis 1, Child grade A 1, grade B 7 and grade C 2) and previous TIPSS for recurrent variceal haemorrhage were studied. At routine portography for assessment of shunt function, portal blood flow was measured using a reverse thermodilution catheter introduced through the shunt into the portal vein. This catheter was then placed in the renal vein through the femoral vein. An angioplasty balloon was used to occlude the shunt and serial changes were recorded in the heart rate, mean arterial pressure, right atrial pressure, portal pressure gradient (PPG), renal vein pressure and renal blood flow (RBF), before, at 2 minutes intervals for 12 minutes following TIPSS occlusion and after deflation of the balloon. Blood was sampled for atrial natriuretic peptide, catecholamines, renin activity, angiotensin 2, endothelin and cyclic GMP from the renal vein and the right atrium prior to and following shunt occlusion. Results were expressed as means and standard error and correlations were sought between the changes in the renal blood flow and the above parameters.

Results: None of the patients had ascites or clinically evident renal failure and were on no vasoactive medications. Baseline mean portal vein flow was 674.3 ml/min and this correlated inversely with renal vein flow (r=0.66, p<0.05). The results of haemodynamic changes are summarised in the table below.

TEST	Pre occlusion	4 min after occlusion	10 min after occlusion	2 min after balloon deflation	*p 1	*p 2
PPG	8.3 (0.7)	42.3 (3.9)	44.5 (3.4)	8.6 (0.4)	<0.001	<0.001
Heart rate	80 (3.6)	77.2 (4.9)	74.5 (4.5)	76 (4.6)	ns	ns
Mean arterial pressure	96 (3.6)	91 (3.1)	86.6 (2.1)	91 (2.8)	ns	ns
Right atrial pressure	2.4 (1.3)	1 (1.2)	1.1 (1)	2.6 (1.2)	ns	ns
Renal blood flow ml/min	289 (32)	166 (26)	169 (29)	326 (42)	<0.002	<0.001

p1-difference between pre and post TIPSS occlusion. p 2-difference between occlusion and release.
*p - t-test

Results of the hormonal analysis are awaited. Changes in the renal blood flow correlated significantly only with the change in the portal pressure gradient (r=0.72, p<0.03).

Conclusions: The results of this study indicate that (a) there is an inverse correlation between portal flow and RBF (b) a significant reversible reduction in RBF occurs with acute increase in the portal pressure gradient and (c) this change in the RBF correlates with the change in the PPG. These changes may be mediated by the hepatorenal reflex and may serve as a model of studying this phenomenon further.

W35

Cerebral and Liver function following TIPSS: A prospective study
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Clinical encephalopathy following the transjugular intrahepatic portosystemic shunt (TIPSS) occurs in 10-20% patients. This study was designed to assess changes in (a) psychometric function and (b) liver function (c) relationship between these following TIPSS.

Methods: Twenty nine patients with TIPSS, (M:F=19:10, mean age 54.3(se 1.6)) were studied. Six were Childs grade A, 16 were grade B and 7 were grade C. Patient who were clinically encephalopathic either prior to or following TIPSS were not included in the study. Serial changes in the liver function tests (ALT, bilirubin, albumin and PT) and psychometric function (Hospital Anxiety Depression scale(HAD), Rivermead Behavioural Memory Test (RBMT), Quality Of Life (QOL) and Cambridge Automated Neurological Test Assessment Battery (CANTAB)) were measured before, 1mo, 3mo, 9 mo and 15 mo following TIPSS. ICG clearance was measured in 17 patients before, 1 and 12 weeks after TIPSS.

Results: Sixteen patients were clinically encephalopathic prior to TIPSS and 7 others became encephalopathic afterwards (12.5%). Portal pressure gradient was 23.2(1.4), 11.1(1.6), 11.8(1.1), 12.8(1.8) and 13.2(2) mmHg at the above time points. Results for psychometric tests and liver function are summarised below.

Results of psychometric analysis:

TEST	PRE	1 Mo	3 Mo	9 Mo	15 Mo
RBMT*	35 (2.2)	37.7 (2.5)	37.6 (2.1)	32.3 (1.3)	36.8 (2.5)
HAAD*	10.3(1.9)	7.9 (1)	7.3 (1.2)	8.1 (1.5)	34.5 (1.9)
QOL*	47.2(3.4)	50.1 (3.3)	46 (3)	51.2 (4.4)	47.9 (3.9)
CANTAB*	1662(153.1)	1724.1 (182.7)	1757 (83.1)	1769(109.7)	1696(147)

* Serial changes were not statistically significant using paired t-test

Results of liver function:

TEST	PRE	1 Wk	1 Mo	3 Mo	9 Mo	p - 1	p - 2
ALT	40 (5)	74(10.8)	37 (5.1)	31 (2.9)	27 (1.8)	<0.01	<0.01
Bil.	43 (5)	102(23)	82 (24)	66(18.9)	58.3 (19)	<0.01	<0.01
ALB	30.7 (1)	30.9 (1)	32 (1)	32 (1.4)	30 (1.6)	ns	ns
PT	18 (1.3)	19 (2.1)	19 (2.4)	17 (3.1)	17 (2.1)	ns	ns
ICG ml/min	302 (40)	231 (35)	-	304 (39)	-	<0.01	<0.01

p - 1- difference between pre and 1 week, p-2- difference between 1 week and 1 month, paired t-test.

No significant correlations were found between changes in the liver function and cerebral functions using linear regression.

Conclusions: The results of this study indicate that (a) psychometric function in cirrhotics is significantly worse than normal individuals but does not deteriorate significantly following TIPSS (b) TIPSS is associated with a reversible deterioration in liver function (c) no significant correlation was found between changes in the cerebral function and the liver function tests.

W36

MICE WITH HOMOZYGOUS DISRUPTION OF THE MDR2 P-GLYCOPROTEIN GENE; AN ANIMAL MODEL FOR STUDIES OF NONSUPPURATIVE INFLAMMATORY CHOLANGITIS AND HEPATOCARCINOGENESIS Carin M.J. van Nieuwkerk, Thais H. Mauad, Koert P. Dingemans, Jaap J.M. Smit, Alfred H. Schinkel, Robbert G.E. Notenboom, Marius A. van den Bergh Weerman, Ronald P. Verkruijsen, Bert K. Groen, Ronald P.J. Oude Elferink, Piet Borst, and G. Johan A. Offerhaus; Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

The mouse *mdr2* gene (and its human homologue *MDR3*, also called *MDR2*) encodes a P-glycoprotein that is present in high concentration in the bile canalicular membrane of hepatocytes. 129/OlaHsd mice with a homozygous disruption of the *mdr2* gene (-/- mice) lack this P-glycoprotein in the canalicular membrane. These mice are unable to secrete phospholipids into bile, showing an essential role for the *mdr2* P-glycoprotein in the transport of phosphatidylcholine across the canalicular membrane. The complete absence of phospholipids from bile leads to a hepatic disease, which becomes manifest shortly after birth and shows progression to an endstage in the course of three months. The liver pathology is that of a nonsuppurative inflammatory cholangitis with portal inflammation and ductular proliferation, consistent with toxic injury of the biliary system from bile salts unaccompanied by phospholipids. Thus, the *mdr2* (-/-) mice can serve as an animal model for studying mechanisms and potential interventions in nonsuppurative inflammatory cholangitis (in a generic sense) in human disease, be it congenital or acquired. When the mice are 4-6 months of age, preneoplastic lesions develop in the liver, progressing to metastatic liver cancer in the terminal phase. The *mdr* (-/-) mice therefore also provide a tumor progression model of value for the study of hepatic carcinogenesis. Interestingly, also in this regard the model mimicks human disease, since chronic inflammation of the biliary system in man may similarly carry increased cancer risk.

W37

HEPATIC EXPRESSION OF PROINFLAMMATORY CYTOKINES IN NEEDLE LIVER BIOPSIES DETECTED USING HOT-START REVERSE TRANSCRIPTASE PCR.
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Expression of proinflammatory cytokines eg. interleukin (IL) 1 α , 1 β , IL-4, tumour necrosis factor α (TNF) and interferon γ (IFN γ) within the liver may be important in the development of hepatic inflammation. Studies looking at blood levels of proinflammatory cytokines have produced conflicting results.

Methods: We therefore assessed the expression of IL-1 α , IL-1 β , IL-4, TNF and IFN γ in 20 consecutive needle liver biopsies using reverse transcriptase PCR (RT-PCR). A portion of the liver biopsy was frozen in liquid nitrogen and stored at -70 $^{\circ}$ C. Preparation of total RNA was followed by cDNA synthesis using AMV reverse transcriptase and oligo(dT) primers. Using CLONTECH amplimers for IL-1 α , IL-1 β , IL-4, TNF and IFN γ , reactions were heated initially at 94 $^{\circ}$ C for 5 minutes before addition of Taq DNA polymerase followed by 35 cycles of the following program: 94 $^{\circ}$ C 45sec; 60 $^{\circ}$ C 45sec and 72 $^{\circ}$ C 2min. PCR products were visualised by ethidium bromide staining after electrophoresis in 1.8% agarose gels. PCR of β actin was used as a control. Indication for biopsy was post liver transplantation (7), abnormal liver function tests (6), alcohol excess (4), chronic viral hepatitis (2) and high AFP (1).

Results: 60% of biopsies expressed TNF, 40% expressed IFN γ and 25% of all biopsies expressed both TNF and IFN γ . 15% of biopsies expressed IL-1 α and in all these biopsies TNF was also expressed but not IFN γ . IL-4 was expressed in only 1 biopsy and was the only cytokine detectable. No cases expressed IL-1 β and in 2 cases no cytokine transcripts were detectable. All cases expressed β actin. There was no cytokine profile specific for biopsies obtained post-transplantation or in patients with histological cirrhosis.

Conclusions: RT-PCR can be used to assess the proinflammatory cytokine profile in needle liver biopsies. Most commonly TNF and IFN γ are expressed but the cytokine profiles observed were not specific for a disease process.

W39

Ultrasound - a non-invasive method of assessing disease severity in primary biliary cirrhosis (PBC) A.G. Lim, R.P. Jazrawi, J.D. Maxwell, T.C.Northfield, A.E.A.Joseph*. Depts of Gastroenterology and Radiology*, St George's Hospital Medical School, London.

Liver biopsy is essential to diagnose PBC. However, repeated biopsies are unsuitable as a method of monitoring disease progression and are liable to sampling error. Patients with early disease may benefit from medical treatment, whereas those with late disease should be considered for liver transplantation. Our aim was to assess whether ultrasound (USS) can differentiate between patients with early and late PBC.

26 biopsy proven PBC patients (24 female, age range 42-76 years) were prospectively studied. 15 had early disease (stage I, n=9; stage II n=6) and 11 had late disease (stage III, n=6; stage IV, n=5). Ultrasound was performed by a single operator who had no prior knowledge of the histology. Liver and spleen size, presence of hepatic fibrosis and regenerating nodules, and features of portal hypertension were recorded. Hepatic fibrosis was recognised by presence of focal, high amplitude (pinhead) echos. Regenerating nodules were recognised as 2-4mm hypoechoic focal lesions, partially or completely surrounded by an echogenic ring. Patients were classified as having early (no fibrosis/regenerating nodules) or late disease (marked fibrosis/regenerating nodules).

The results of ultrasound and histology were concordant in 14 out of 15 with early and in 10 out of 11 with late PBC ($\chi^2=17.22$, $p<0.0001$). Increased hepatic echogenicity and the presence of regenerating nodules were good markers of cirrhosis.

USS can differentiate between early and late PBC. Repeated USS follow up of PBC patients would be valuable for monitoring disease progression. Its non-invasive nature is likely to give it high patient acceptability.

W38

ω -3 AND ω -6 FATTY ACIDS UPREGULATE IL-6 STIMULATED HEPATOCYTE ACUTE PHASE PROTEIN PRODUCTION *IN VITRO*.
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Fatty acids (FA) have been used therapeutically to improve nutrition and immune function in weight-losing cancer patients. This study attempts to elucidate the effect of FA's on the production of acute phase proteins (APPs) by isolated human hepatocytes *in vitro*.

Methods
Human hepatocytes were isolated from resection specimens by perfusion and enzymatic digestion. FA free bovine serum albumin (BSA) was complexed in equimolar concentrations with γ -linoleic acid (GLA), eicosapentaenoic acid (EPA), oleic acid (OA), palmitic acid (PA), docosahexaenoic acid (DHA) and arachidonic acid (AA). FA's were added in varying concentrations, in the presence and absence of a fixed dose of IL-6 (1ng/ml), to primary hepatocyte cultures and the resultant APPs measured by ELISA.

Results
BSA complexed GLA and EPA significantly upregulated IL-6 stimulated production of C-reactive protein (CRP), α -1 antichymotrypsin (ACT) and downregulated haptoglobin and prealbumin. Changes in APP production in the absence of IL-6 were not significant.

	CRP % change	ACT % change	Prealbumin % change	Haptoglobin % change
EPA (5 μ M)	+650*	+120*	-38†	-49†
GLA (5 μ M)	+580*	+160*	-42†	-30

* $p<0.01$ † $p<0.05$

These results demonstrate that FA's exert a profound upregulatory influence on IL-6-stimulated APP production by isolated human hepatocytes which contrasts with the proposal that they may reduce APP production *in vivo*.

W40

N-ACETYL CYSTEINE (NAC) IS A POTENT PERIPHERAL VASODILATOR
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NAC's action on peripheral vasculature was previously unknown *in vivo*. Six patients with biopsy proven cirrhosis (4 ALC; 2PBC; 5 Childs Pugh A; 1 B: mean age 60.7 $\pm$ 2.5 years) and six age (56 $\pm$ 2.3 years) and smoking status matched controls were given NAC via a cannula placed in the brachial artery of the non-dominant arm and a cumulative dose response curve (using a maximum of 1/100th of the standard systemic dose of NAC) of forearm blood flow (measured by indium-gallium in silastic strain gauges) in both the infused and control arms was obtained for each subject.

Intraarterial dose NAC (mg/min)	CONTROLS		CIRRHOTICS	
	Control arm	Infused arm	Control arm	Infused arm
0	3.58	4.17	3.02	3.00
1	3.58	3.83	2.86	3.00
3	3.41	3.67	2.82	3.00
10	2.75	3.39	2.55	3.69
30	2.46	* 3.52	2.69	3.68
100	2.70	* 5.85	2.78	* 6.24
300	2.85	* 8.11	3.14	* 12.72

* = significant difference at least at the 95% level

No significant difference was seen between the forearm blood flow ratios or percentage change in flow in response to NAC in the control group and cirrhotic patients, but more patients with more severe liver disease need to be studied before a difference can be excluded.

W41

PHARMACOKINETICS OF N-ACETYL-CYSTEINE (NAC) ARE ALTERED IN CHRONIC LIVER DISEASE.

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9 biopsy proven cirrhotic patients (of various Childs' Scores) and 6 healthy, age-matched controls were each given 600mg NAC as an intravenous bolus. Venous samples were taken at 0, 20, 40, 60, 90, 120, 180, 240, 360 and 480 minutes thereafter and plasma NAC concentration was assayed by a modification of the high performance liquid chromatographic method of Lewis et al, 1984. Each pharmacokinetic curve fitted a two compartment model. Mean results (+/- standard deviation):

	t1/2 el	AUC	Clr tot	Vdss
Controls	3.25	106.1	5.84	18.8
n=6	(0.80)	(21.8)	(1.10)	(6.8)
Patients	4.25	197.4	3.74	17.9
n=9	(1.22)	(103.6)	(1.64)	(9.5)
t-test	p>0.05	p<0.05	p<0.01	p>>0.5

t1/2 el is the elimination half-life in hours, AUC is the area under the curve in mg/L x hours, Clr tot is the total clearance in L/hour and Vdss is the volume of distribution in litres at "steady state".

There was a significantly reduced clearance of NAC by patients with cirrhosis of normal controls. The t1/2 elimination just failed to reach statistical difference between the two groups. Patients with suspected chronic liver disease, unlike those with acute liver damage due to paracetamol (Prescott et al, 1989), may be more likely to develop adverse reactions to NAC as these occur when plasma NAC concentration is highest.

W43

A comparative study of TIPSS and oesophageal transection in the management of uncontrolled variceal haemorrhage. Jalan, R., *John, T.G., *Redhead, D.N., *Garden O.J., Finlayson N.D.C., Hayes, P.C. Centre for Liver and Digestive Diseases, Dept. of *Surgery and *Radiology, Royal Infirmary of Edinburgh

Variceal bleeding in cirrhosis is associated with mortality rates in excess of 50% and increases with every subsequent bleed. Transjugular intrahepatic portosystemic stent-shunts (TIPSS) have been shown to reduce portal hypertension consistently and has recently been reported to arrest active variceal haemorrhage. This study compares the results of TIPSS with oesophageal transection and devascularisation in patients with uncontrolled variceal haemorrhage admitted to a single centre with an interest in variceal bleeding.

Methods: Two hundred and sixty cirrhotic patients have been referred with variceal bleeding over the past 7 years. In 41 patients (15.8%) haemorrhage was uncontrolled despite 2 treatments with sclerotherapy. Thirty eight patients were eligible for analysis. Nineteen were considered for surgery (1988-1991) and 19 for TIPSS (1991-1994). Both groups were well matched for age, sex, aetiology of liver disease, its severity and complications. They have been followed up for 13 patient years (TIPSS-7, longest 20 months; surgery-6, longest 23 months). Survival and rebleeding were analysed using the Kaplan Meier method.

Results: Seven of the 19 were considered unfit for surgery and 12 underwent oesophageal transection and devascularisation. TIPSS was undertaken successfully in 17 patients, using the Palmaz stent in 4 and the Wallstent in 13. Successful TIPSS reduced the mean portal pressure gradient from 22.2 (se 1.2) to 9.7 (se 0.7) mm Hg (p <0.001). Mortality within 6 weeks of the initial bleed was 42% after TIPSS compared with 79% after surgery (p<0.05). Rebleeding occurred in 15.6% patients with TIPSS as compared with 41.6% in the surgery group (p<0.05). Encephalopathy in the patients leaving the hospital was not significantly different (TIPSS 22.2% and surgery 25%). TIPSS was followed by active infection in 20% compared with 36% following surgery.

Conclusions: The results of this study indicate that the overall mortality in this group patients is high whatever the type of treatment used. TIPSS can be performed successfully in these patients who are often not considered candidates for surgery. Rates of rebleeding and mortality are significantly lower in patients treated by TIPSS compared with surgery and we believe, that TIPSS should now be regarded as the treatment of choice for uncontrolled variceal haemorrhage.

W42

Ursodeoxycholic acid (UDCA) improves hepatic excretion in primary biliary cirrhosis (PBC). A.G.Lim, R.P.Jazrawi, J.D.Maxwell and T.C. Northfield. St George's Hospital Medical School, London.

It has been postulated that UDCA reduces cholestatic liver damage in PBC. Measurement of hepatic uptake and excretion rates are indices of hepatocellular function and cholestasis respectively. Our aim was to assess the effect of UDCA on these functions in PBC.

20 patients with biopsy proven PBC (18 female, aged 42-73) were randomised in a double blind fashion to receive either UDCA at 12-15 mg/kg (n=9) or placebo (n=11). Hepatic uptake and excretion rates were assessed by first giving patients an intravenous bolus of ^{99m}Tc HIDA and then analysing the kinetics of its plasma disappearance. These analyses together with routine liver function tests were performed before and after 3 months of treatment.

At the beginning of the study, there were no significant differences in these parameters between patients on UDCA and those on placebo. However, after 3 months, hepatic excretion rate in the UDCA group had improved from 1.17(±0.14) to 1.33(±0.11) % dose/min, p<0.03. Hepatic uptake rates remain unchanged. Levels of alkaline phosphatase (p<0.01), γ-glutamyl transpeptidase (p<0.002) and bilirubin (p<0.05) also improved on UDCA. No significant changes were seen in hepatic uptake or excretion rates or in liver function tests in the placebo group.

We have demonstrated that UDCA improves hepatic excretion rate in PBC. Reduction of cholestasis is likely to be an important mechanism of its action in PBC.

Oesophagus W44-W57

W44

MAPPING THE CORTICAL CENTRES FOR SWALLOWING IN MAN: EVIDENCE FOR HEMISPHERIC DOMINANCE

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Background: Studies of dysphagia following stroke suggest that the cortex plays an important role in swallowing control but do not explain why unilateral lesions produce varying swallowing abnormalities. Aims: To map the cortical centres for the buccal (B), pharyngeal (P) and oesophageal (O) phases of human swallowing and to determine their relative hemispheric preponderance. Methods: 5 healthy volunteers were studied. Handedness was scored using the Edinburgh Inventory. The phases of swallowing were recorded using surface electrodes on the buccal mylohyoid muscles (B Phase) and intraluminal bipolar electrodes in the pharynx (P Phase) and oesophagus (O Phase). Transcranial magnetic stimulation was applied at 1.9±0.25 tesla to sixty points on a 10 by 6cm scalp grid bilaterally. The EMG amplitudes for each phase were recorded, and topographic maps were then coregistered with MRI brain images. Results: Topography: All individuals showed discrete cortical representation for each phase. The B phase had the largest representation, its locus being situated in the pars opercularis of the inferior frontal gyrus. The loci for P and O phases were situated in the anterior aspects of the inferior and middle frontal gyri respectively. Dominance: The B phase always lateralised to one hemisphere; 3 individuals showing right, and 2 left sided dominance. The P and O phases always lateralised to the same hemisphere; 3 subjects showing left and one right sided dominance. One individual showed bilateral control of the P and O phases. For each phase the degree of dominance ranged from 2-10 fold (Mann-Whitney C.I>95%). The hemispheric dominance for the B phase was independent of that for the P and O phases with no association between hemispheric dominance and handedness score. Conclusions: The control centres for the phases of human swallowing have separate cortical representation with inter-subject variation in dominance, independent of handedness. These data explain the variation in swallowing dysfunction after stroke and lay the foundation for objectively evaluating brain-gut motor control in cortical disease.

W45

THE ASSESSMENT OF TRANSIT EFFICIENCY OF A SWALLOWED BOLUS AS A MEASURE OF OESOPHAGEAL MOTOR FUNCTION. P Cherian, M Smith, KD Bardhan, B Dawson, S Heely. Rotherham General Hospitals NHS Trust, Moorgate Road, ROTHERHAM, S. Yorks. S60 2UD

Introduction Measurement of radio-labelled solid bolus transit gives a physiological measure of oesophageal function not often reflected by standard manometry, pHmetry and barium oesophagogram. **Method** 10MBq99mTcTin colloid was cooked into 10ml egg white and subjects chewed and swallowed 2 boluses sitting upright. Sequential gamma camera images were taken. The effectiveness of bolus transport was ascertained using an index Transit Efficiency(TE) values >70% being normal. Young (<40y) and middleaged (>40y) volunteers and patients with a variety of symptoms (reflux, dysphagia, noncardiac chest pain [NCCP]) were investigated. Patients with proven achalasia were chosen as positive controls.

	n	TE<70%	Abnormal findings in:		
			Endoscopy	Manometry	pH
Volunteers <40y	11	0%	{ Not done		
Volunteers >40y	24	75%			
Reflux	37	62%	35%	33%	85%
Dysphagia	37	65%	33%	55%	17%
Reflux + dysphagia	14	71%	36%	25%	75%
NCCP	64	47%	14%	32%	67%
Achalasia	10	100%	-	100%	-

Summary & Conclusions Transit efficiency decreases with age. This is probably a new observation. However, it is in symptomatic patients that significant hold up is seen. There is only broad correlation with other oesophageal tests. This is expected as they measure different aspects of oesophageal function. The test may be useful in sequential studies of oesophageal transit function.

W46

INVESTIGATION OF GASTRO-OESOPHAGEAL REFLUX AND ACID SECRETION IN PATIENTS UNRESPONSIVE TO THERAPEUTIC DOSES OF OMEPRAZOLE. S S Kadiramanathan, D F Evans, and D L Wingate. Gastrointestinal Science Research Unit, London Hospital Medical College, London.

Approximately 10 to 20% of patients with gastro-oesophageal reflux disease (GORD) respond poorly to anti-reflux medication, including high dose acid suppression. Specific reasons for these failures remain unclear but sub-optimal acid suppression may be an important factor. This study presents the results of 24 hour, ambulatory, dual channel pH monitoring in GORD patients regarded as treatment failures.

Twenty patients (10m, 10f, age 16-67y), representing 9.4% of 213 referred for investigation of gastro-oesophageal reflux (GOR) in our hospital over a period of 24 months, underwent oesophageal manometry and dual channel, gastric and oesophageal ambulatory pH monitoring whilst taking omeprazole (OM) 20mg (n=9) or 40mg (n=11). Nine had oesophagitis and two hiatus hernia. One patient had previous fundoplication and another, balloon dilatation for achalasia. All were symptomatic in spite of treatment with OM for at least 3 months. A dual channel pH probe was positioned with one sensor in the stomach, 10 cm distal to the manometrically defined lower oesophageal sphincter (LOS) and the 2nd sensor 5 cm above the LOS. GOR and gastric pH were expressed as % time <pH4.

RESULTS:
MANOMETRY. The median LOS pressure was 8.3 mmHg (range 1.7 - 26.3) which is consistent with patients with GORD.

pH (% time <pH4)	OESOPHAGEAL		GASTRIC	
	Median	Range	Median	Range
Omeprazole 20 mg	9.9%	0-15.3	50.5%	5.1-94.9
Omeprazole 40 mg	1.4%	0-58.8	37.9%	15.1-75.3

All patients were symptomatic during studies although symptom correlation was variable between 10-100%, again typical for GORD. Seven patients underwent laparoscopic Nissen fundoplication, the remainder continue with antisecretory drugs pending review.

Dual pH monitoring has confirmed reduced, but continuing reflux caused by inadequate acid suppression in spite of long-term therapy with OM. These studies highlight the importance of objective measurements in patients who respond poorly to, or who relapse whilst on therapy. Dual channel pH studies can be very useful in titrating the correct dose of OM for optimal acid suppression. This study also illustrates that patients can have GORD even when they do not respond to proton pump inhibitors.

W47

TUSSIVE EFFECT OF CAPSAICIN IN SYMPTOMATIC GASTROESOPHAGEAL REFLUXERS WITHOUT COUGH

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A pathological gastro-oesophageal reflux (GOR) has been reported in 4-21% of patients with chronic cough. Aim of this study was to clarify the influence of GOR on cough threshold in patients with digestive symptoms but free from respiratory involvement. Out of 57 consecutive subjects referred for 24 hour oesophageal pH monitoring because of digestive reflux symptoms, 29 were studied by pH monitoring, manometry, upper gastrointestinal endoscopy, pulmonary function tests and capsaicin challenge. Capsaicin is the active component of red pepper; cough threshold was evaluated by inhalation of increasing doses of capsaicin from 0.3 up to 9.34 nmol, expressing the results as the dose of capsaicin eliciting 5 coughs (PD5). Aereosols were delivered by a yet nebulizer attached to breath actuated dosimeter. Statistical analysis was performed by the Student's t test after log transformation or by the χ^2 test. **RESULTS:** 14/29 patients were considered refluxers on the basis of a total oesophageal acid exposure time above 4.7%. Oesophagitis grade 0 was found in 15, grade 1 in 7, grade 2 in 7 patients. PD5 was significantly lower in refluxers (1.8 ± 5.2 nmol, $\pm$ SD) than in non-refluxers (13.5 ± 8.6 nmol) ($p<0.001$; Student's t test); there was no difference in ventilatory parameters between the two groups. All patients with a pathological acid exposure time but one had a low cough threshold, irrespective of the grade of the esophagitis. **IN CONCLUSION** 1) GOR patients without respiratory symptoms have a reduced cough threshold; 2) the enhanced cough response to capsaicin is due to acid reflux rather than to esophagitis; 3) the acid reflux seems to be only a cofactor of cough and not a fully causative agent.

W48

CAUSES OF PATHOLOGICAL OESOPHAGEAL ACIDIFICATION AFTER PNEUMATIC LOS DILATATION IN ACHALASIA

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Reflux oesophagitis has been reported in 7-50% of achalasic patients after myotomy, in 1-7 % after dilatation of the cardias. A complete disruption of LOS tone is the most widely accepted explanation, but slow clearance of refluxed acid or delayed gastric emptying represent alternative hypotheses. To clarify the mechanisms associated with a pathological reflux, we studied 22 achalasic patients 1-6 months after pneumatic dilatation (Rigiflex achalasia dilator, 3.5 cm diameter, inflated twice to 300 mmHg for 1 minute). For the patient to enter the study, the procedure had to be successful both clinically (good or excellent results according to the Vantrappen's criteria) and radiologically (normal oesophageal progression of a solid bolus, if the case after 50 ml of water). This took place after the 2nd and the 3rd dilatation in 6 and 3 patients respectively. All patients underwent the following examinations: SPT measurement of LOS pressure (nv >10 mmHg); gastric emptying rate of a solid meal by real-time ultrasonography (nv <300 min); total acid exposure time (nv <4.7%) and mean acid clearance time (nv <2.6 min) by 24-hour pH monitoring; analogic-visual hearthburn scale. Acid exposure time was pathological in 5/22 patients, gastric emptying in 13, LOS pressure in 7. Dividing the patients according to their normal (N) or pathological (P) reflux state, no difference was found in gastric emptying (N 325 ± 23 min vs P 284.6 ± 50.6 , $\pm$ SEM, NS) or LOS pressure (N 14.9 ± 1.3 mmHg vs P 13.8 ± 2.5 , NS). On the contrary, a significant delay in oesophageal acid clearing was found in patients with pathological reflux (N 2.5 ± 1.1 min/reflux vs P 15.9 ± 4.5 , $p<0.05$). The hearthburn score was similar in patients with or without postdilatation reflux and was markedly improved after the dilatation. **In conclusion**, in dilated achalasic patients the main factor of a pathological reflux is a deranged clearing capacity. An excessive disruption of lower oesophageal sphyncter plays no role in causing a pathological reflux; a further dilatation might, paradoxically, help.

W49

GASTRIC EMPTYING OF SOLID MEAL IN PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX

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The role of a delayed gastric emptying in pathological gastro-oesophageal reflux (GOR) is debated, different Authors reporting opposite results. This is probably due to the use of liquid or semisolid labelled food. Aim of our study was to clarify gastric emptying of a "realistic" solid meal in GOR. The study was performed in 25 GOR patients (15 with dyspepsia, D, 10 without, ND) and in 28 healthy subjects (C) of similar age and sex. All GOR patients were submitted to gastroscopy, ultrasonographic measurement of gastric emptying of a solid meal (pasta, meat sauce, bread, ham, fatty cheese; 800 Cal, 15% from protein, 40% from carbohydrates, 45% from fat) and 24 hour pH-monitoring. The ANOVA and paired Student's t tests were used for analysis.

RESULTS: Gastric emptying in healthy controls was (mean $\pm$ 1 SEM) 209 $\pm$ 10.4, range 87-319 min. GOR patients had a significant delay in gastric emptying (307.6 $\pm$ 21 min; $p < 0.001$ vs controls); there was no difference in gastric emptying in GOR patients with and without dyspepsia (318 $\pm$ 30.6 min vs 292 $\pm$ 26.6, respectively) (figure); 14/25 GOR patients had gastric emptying within normal range; there was no difference in total, diurnal, postprandial and nocturnal oesophageal acid exposure time between patients with normal and delayed gastric emptying.

IN CONCLUSION: gastric emptying of a physiologic solid meal is markedly delayed in patients with pathological GOR. This delay is not related to the degree of reflux or to the presence of dyspepsia.

Group	Mean (min)	SEM (min)
ND	209	10.4
D	307.6	21
C	209	10.4

W50

THE EFFECT OF HEALING OF OESOPHAGITIS ON PATIENT QUALITY OF LIFE

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Aim: To perform one of the first ever assessments of the effect of healing oesophagitis with omeprazole (OME) on quality of life (QOL).

Methods: Consecutive attenders at two endoscopy lists with grade II-III oesophagitis (modified Savary-Miller) were treated with OME 20mg BD for 8 to 12 weeks. Before and after treatment all patients completed a detailed symptomatic questionnaire and the Short Form-36 (SF-36) general health survey questionnaire. Those patients whose oesophagitis had not healed endoscopically after 12 weeks treatment were excluded.

Results: Four of the 32 patients enrolled failed to heal after 12 weeks treatment and 1 patient withdrew due to side effects, giving a healing rate of 84%. Of the remaining 27 patients (15 male, mean age 49 yrs, range 28-74 yrs), 20 had grade II oesophagitis and 7 grade III. All 5 patients who failed to heal had grade II oesophagitis. Before treatment all patients had heartburn at least daily (20 patients) or weekly (7), and after treatment all patients said they rarely (14) or never (13) had heartburn. All 8 parameters of quality of life measured by the SF-36 improved after healing of oesophagitis, with the change being statistically significant for both bodily pain and vitality (see table).

	Physical Funct.	Role-Physical	Bodily Pain	Gen. Health	Vitality	Social Funct.	Role-Emotion	Mental Health
Before	76.3	61.1	57.1	64.6	46.3	64.0	78.9	73.9
After	81.3	70.4	70.7*	68.8	55.2*	64.1	86.3	76.9

* $p < 0.05$ and * $p < 0.01$ (Wilcoxon Matched-Pairs Signed-Ranks Test)

Conclusion: Treatment of grades II-III oesophagitis with omeprazole 20 mg BD for 8-12 weeks not only heals 84% of patients but significantly improves 2 of 8 measured parameters of quality of life, namely bodily pain and vitality. Larger numbers are required to assess the effect on patients whose oesophagitis is not healed by the same treatment.

W51

COMPARISONS OF MANUAL AND AUTOMATED ANALYSIS OF OESOPHAGEAL BODY CONTRACTILITY WITH ON-LINE AND COMPRESSED DATA.

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The quantity of data collected during 24-hour oesophageal pressure recording is too great for routine manual analysis or storage.

This study compared manual analysis of on-line data by 2 operators (A1 with A2), and with automated analysis of both on-line (A3) and compressed data (A4) (Gaeltec).

Sixteen healthy controls were given 10 swallows (5ml bolus). Oesophageal pressures were recorded at 15, 10 and 5cm above the lower oesophageal sphincter (LOS). On-line sampling was at 8 samples/sec. Stored data was compressed by a factor of between 2 to 16 depending on the subject's activity.

The mean value and the standard deviation for each patient and for each analysis were calculated. Analysis of variance showed no significant difference between the 4 analyses for the amplitude of contraction measured at 3 levels or the progression velocity or the duration of contraction at 2 levels, only the duration of the contraction at 15cm (D15cm) above the LOS was significantly different ($p = 0.001$). Post-hoc comparisons (Tukey's test) on D15cm found that the automated analysis on the compressed data (A4) differed from the other 3 analyses ($p = 0.001$). The means of D15cm derived by the 4 analyses were A1=2.37sec; A2=2.43sec; A3=2.5sec; A4=2.76 sec. (The difference between the means did not exceed 0.5 second).

The within-subject variation was calculated and an average of these values was tabulated for each of the analyses (A1, A2, A3 and A4). Using Bartlett's test no significant difference between analysis variation was found for each of the pressure parameters ($p > 0.05$).

Conclusion: This study showed the 4 analyses of pressure parameters did not differ from each other except for the duration (D15cm). Clinically the difference of less than 0.5 seconds in duration of contraction is small. Therefore these results indicate that this method of data storage and automated analysis is a valid method for long-term oesophageal pressure recording.

W52

THE IMPACT OF SMOKING CESSATION ON SALIVARY BICARBONATE AND EPIDERMAL GROWTH FACTOR

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Saliva is an important determinant of intra-oesophageal acid neutralisation and smoking is known to reduce salivary flow, bicarbonate concentration and salivary epidermal growth factor (EGF) output. We have therefore studied the effect of smoking cessation on salivary function.

Twenty four asymptomatic smokers were studied (11 male, median age 45 (range 22 - 58) years, 15 (5 - 40) cigarettes per day for 23 (1 - 40) years). Six subjects continued to smoke and eighteen attempted smoking cessation. Salivary function and urinary nicotine metabolites were measured at 0, 7 and 21 days.

Of eighteen subjects attempting smoking cessation, six defaulted, six failed and six were successful. Smoking cessation was associated with an increase in salivary bicarbonate concentration at day 7 (4.9 (1.1 - 5.7) mmol L⁻¹ versus 6.3 (2.9 - 9.0) mmol L⁻¹, $p = 0.028$), sustained at day 21 ($p = 0.028$), an increase in salivary flow (0.37 (0.13 - 0.70) ml min⁻¹ versus 0.58 (0.17 - 0.78) ml min⁻¹, $p = 0.028$), but no significant change in salivary EGF output (0.53 (0.32 - 0.76) ng min⁻¹ versus 0.51 (0.44 - 0.9) ng min⁻¹).

Smoking cessation increases salivary flow and bicarbonate secretion and facilitates intra-oesophageal acid neutralisation.

W53

FIBRINOGEN CONCENTRATION IN OESOPHAGEAL CANCER

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Patients with oesophageal cancer were noted to have raised plasma fibrinogen concentrations during there assessment for surgery. A prospective controlled study was performed over a twelve month period to assess the significance of this finding. Thirty controls (Group 1) and twenty nine consecutive patients with oesophageal carcinoma (Group 2) had estimations of plasma fibrinogen prior to any treatment. Account was taken of smoking habit in each case and patients were excluded if there was a pre-existing cause for hyperfibrinogenaemia.

Group 2 patients had significantly higher fibrinogen levels than Group 1: Group 1 median 3.0 (range 2.1-4.0) g/l, Group 2 5.2(3.0-9.7) g/l; $P<0.001^*$. Group 2 was subdivided and analysed using the TNM classification to determine stage at presentation: there was no significant difference between T1, T2 and T3 groups. Patients with T4 tumours had significant higher fibrinogen levels than patients with T1-3 disease: T4 median 6.9(range 5.2-9.7) g/l, T1-3 3.4 (3.0-4.9) g/l; $P<0.001^*$. Patients with nodal disease had significantly higher fibrinogen levels than those without; N0 median 4.00(3.0-6.8) g/l, N1 median 5.40(3.8-8.8) g/l; $P<0.01^*$. Patients with distant metastases had higher fibrinogen levels than those with locally confined malignancy, but this result was not statistically significant.

These results demonstrate that fibrinogen levels are raised in patients with oesophageal cancer. There is a trend for higher fibrinogen levels to be associated with more advanced tumour stage. Fibrinogen estimation may have a role in the assessment of tumour stage in patients with potentially operable oesophageal cancer.

*Wilcoxon Rank Sum Test

W55

OESOPHAGEAL CANCER IN YORKSHIRE: A REGIONAL AUDIT

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During 1990 four hundred cases of oesophageal cancer were reported to the Yorkshire Cancer Registry. The case notes of these patients were the subject of a retrospective audit 3-4 years later.

The patients were initially investigated at 32 different hospitals and 41% were referred on to a second institution. Oesophago-gastroscopy was carried out in 95% of patients and showed that 4% of tumours were in the upper third of the oesophagus, 15% in the middle third, 54% in the lower third and 27% at the cardia. Squamous cell carcinoma was diagnosed in 34% of cases and adenocarcinoma in 66%. Staging investigations were performed in 60% of cases. The remaining 40% were not "staged" before decisions on treatment were made.

A surgical opinion was given in 85% of cases and 49% of all patients were operated upon. Of these, 73% underwent resection of the tumour (potentially curative in 56%, palliative in 44%). Operative mortality was 16%. Radical radiotherapy was the treatment of choice in 3% of patients. Palliative treatment in the form of endoscopic intubation, laser ablation or radiotherapy was given to 33% of patients. 15% of patients did not receive any specific treatment.

Overall 10 (2.5%) of the 400 patients are still alive after 3-4 years. Median survival was 10 months among patients who underwent surgical resection, 12 months among those who received radical radiotherapy and 4 months for those who received palliative treatment. Thus prognosis for patients with cancer of the oesophagus in Yorkshire remains poor. Radical surgery and radical radiotherapy were the only forms of treatment that resulted in survival for longer than 3 years.

W54

THE TREATMENT OF IATROGENIC OESOPHAGEAL PERFORATION WITH COVERED EXPANDING METAL STENTS

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Laser recanalisation is a well established method of palliating patients with malignant dysphagia. The major complication of this form of therapy is iatrogenic oesophageal perforation which is invariably due to pre laser oesophageal dilatation. If recognised at the time, conservative management with intravenous antibiotics and ranitidine together with fine bore nasogastric feeding is successful in 87% of cases but involves prolonged hospital stay. This study reports the results of 6 consecutive patients with this complication treated with covered expanding metal stents.

All 6 cases had biopsy proven lower 1/3 oesophageal carcinoma which had been previously treated by laser on at least 1 occasion. In all cases the cause of perforation was dilatation of the malignant stricture with wire guided bougies prior to laser treatment. This was recognised on endoscopic assessment post dilatation. All patients were treated strictly nil by mouth and the following day, under fluoroscopic control and intravenous sedation, an expanding covered metal stent 20 or 25mm in diameter (Wallstent 4, Gianturco 2) was inserted with the plastic covered section across the perforated segment. The position of the stent was confirmed by contrast swallow the following day and the patient allowed fluids and diet as tolerated. In all cases the patients were discharged within 3 days swallowing at least a soft diet.

In conclusion, this small series demonstrates that treatment of iatrogenic oesophageal carcinoma with expanding covered metal stents is both safe and effective, and reduces hospitalisation by at least 50%.

W56

OESOPHAGEAL CELL ENDOCYTOSIS OF FLUORESCENT MICROSPHERES: A COMPARISON OF NORMAL AND INFLAMED OESOPHAGUS.

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Endocytosis lies at the centre of epithelial cellular metabolism and is a good indication of cellular function. The aim of this study was to determine if oesophageal epithelial cells endocytose, and if this process was altered in oesophagitis.

Methods: Endoscopic oesophageal biopsies from normal and inflamed human oesophagus were placed overnight in organ culture containing fluorescent microspheres of sizes 0.01-0.1µm. Samples examined using confocal- and electron-microscopy showed that 0.01µm and 0.1µm diameter microspheres were endocytosed by oesophageal epithelial cells, passing first to the early endosomes and then to the lysosomal compartment. 1µm microspheres adhered to the cells, but were not phagocytosed. Both the larger, mature squames and the smaller differentiating prickle cells took up the microspheres. The processes could be stopped by incubation at 4°C.

Disaggregated cells were analysed by flow cytometry. The number of microspheres endocytosed was directly related to the concentration in the culture medium. Epidermal growth factor increased the uptake of microspheres epithelial cells. Cells from biopsies with oesophagitis (n=6) endocytosed significantly more microspheres ($p=0.015$) than normal biopsies (n=10). In addition, epithelial cell size in oesophagitis was significantly smaller ($p=0.013$).

Summary: Oesophageal epithelial cells endocytose fluorescent microspheres. This phenomenon is increased in oesophagitis. Cellular micro-particulate uptake may be a physiological clearance mechanism in the oesophagus.

W57

THE COMBINATION OF LASER TREATMENT AND INTRALUMINAL RADIOTHERAPY FOR MALIGNANT DYSPHAGIA

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Laser treatment for malignant dysphagia is limited by recurrent intraluminal tumour requiring repeated treatment at 4 to 8 week intervals. To reduce the need for follow up treatment patients successfully palliated by laser were treated with intraluminal radiotherapy receiving 10-15 Gy at 1 cm from the source as a single treatment with the Selectron system. Patients with squamous cell carcinoma also received external radiotherapy (upto 50 Gy).

30 patients with inoperable oesophageal carcinoma (16 adenocarcinoma and 14 squamous cell) were well palliated by a median of 3 laser treatments prior to radiotherapy. Following the radiotherapy 8 survived a median of 22 (range 4 - 40) weeks without requiring any further endoscopic treatment. The remaining patients survived a median of 34 (range 4 - 102) weeks and required a median of 3 endoscopic treatments. 11 patients developed fibrous strictures with no intraluminal tumour and were treated by dilatation. 11 patients required dilatation and repeat laser therapy for a combination of fibrous stricture and recurrent intraluminal tumour. Six patients eventually required Atkinson tubes.

Intraluminal radiotherapy administered to patients successfully palliated by laser therapy reduces the need for follow up treatment but in many cases leads to fibrous stricture formation.

W59

Study into Ethnic differences in Leicester of Helicobacter pylori in Peptic ulcer disease.

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Introduction:

The South Asian population in Leicester account for 23% of the city's population. A recent Leicester study showed a significantly higher rate of duodenal ulcer disease, ($p < 0.001$), in South Asian patients aged 45 years and over compared to Europeans.

Aims:

To determine the incidence of *H. pylori* in dyspeptic South Asian and European patients.

Methods:

Consecutive dyspeptic patients attending routine endoscopy were studied. At endoscopy antral and body biopsies were obtained for histology, urease testing and 5ml of blood for serology. The biopsies were assessed blind by two experienced pathologists by both H&E and modified Giemsa stains.

Results:

202 subjects participated in the study, of whom 91 were South Asian. A positive diagnosis of *H. pylori* was made, 2 of 3 tests (histology, serology & urease) were positive. *H. pylori* occurred more commonly in the South Asian population, 56 of 91 subjects (62%), compared to 50 of 111 Europeans (45%), $\chi^2 = p < 0.05$.

Conclusion:

South Asians in Leicester have a significantly higher prevalence of *H. pylori* compared to Europeans. The higher incidence of *H. pylori* in the ethnic population may account for the higher levels of duodenal ulcers in the South Asian population. We therefore recommend that the South Asian population in the UK is targeted for *H. pylori* screening and eradication.

Helicobacter pylori W58-W74

W58

COMPARISON OF SERUM AND SALIVARY IMMUNOASSAYS FOR HELICOBACTER PYLORI

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The Cortex Diagnostic Helisal IM Assay test is a quantitative immunoassay for salivary IgG antibodies against *Helicobacter pylori*. It is a simple test that can be performed in the General Practitioner's surgery. 1 ml of saliva is obtained using an absorbent lollipop placed in the mouth for five minutes. The Cortex Diagnostic *H. pylori* (IgG Assay test) is an immunoassay for the measurement of serum IgG antibodies against *H. pylori*. Each patient provided saliva and blood before endoscopy. We compared these two tests with "Gold Standard" evidence of *H. pylori* infection (antral biopsies for urease test, culture and histology) in 86 patients undergoing endoscopy for dyspepsia.

Twenty-seven (31%) patients were *H. pylori* positive. Of these, three had duodenal ulcers and one gastric ulceration. The sensitivity and specificity of the serum antibody Elisa test was 84.6% and 76.9% respectively. The sensitivity and specificity of the saliva Elisa test was 84% and 62.7% respectively for a cut off value of 0.15 log Eu/ml. The negative predictive value of the saliva test was 90.2%, but the positive predictive value was only 48.8%.

In the *H. pylori* positive group there was close correlation between the salivary and serum tests; of the 22 serum positive patients, 21 were saliva positive.

The high negative predictive value of the saliva test using the 0.15 log Eu/ml cut off makes it a useful test for identifying *H. pylori* negative patients in general practice. However, serum testing for *H. pylori* is superior to salivary testing and remains the gold standard serological test in the hospital setting. Salivary testing may be useful in children where venesection is difficult. The cut off value of the saliva test can be changed to obtain the most appropriate sensitivity, specificity and predictive values for the setting in which it is being used.

W60

ERADICATION OF HELICOBACTER PYLORI (Hp) WITH LANSOPRAZOLE AND CLARITHROMYCIN.

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Introduction: Dual therapy eradication rates vary between 0-93%. The dose, frequency & duration of treatment with proton pump inhibitors (PPI) may account for these differences. Lansoprazole, a novel PPI, is a more potent *Hp* bacteriostat, in vitro, than omeprazole. Monotherapy with clarithromycin has an *Hp* eradication rate of about 50%. Different dosing regimens have not so far been studied. The aim of this open, comparative, randomised study was to investigate the efficacy & safety of lansoprazole 30mg od vs bd (2 vs 4 weeks) plus clarithromycin 500mg tds in the eradication of *Hp*.

Methods: 68 patients (44 men, median age 47, range 19-71) were enrolled. 66 had positive *Hp* histology (antrum $\pm$ corpus) and ¹⁴C-urea breath test (¹⁴C-UBT, European standard protocol, positive result = excess δ ¹⁴CO₂ excretion > 5 per ml). Each received clarithromycin 500mg tds for two weeks. They were randomised to also receive lansoprazole 30mg od for 2 (Group 1, n=16) or 4 (Group 2, n=16) weeks, or lansoprazole 30 mg bd for 2 (Group 3, n=18) or 4 (Group 4, n=16) weeks. Eradication of *Hp* was assessed by ¹⁴C-UBT 4 weeks after finishing treatment.

Results: Per protocol analysis (53 patients) shows that *Hp* was eradicated in 6/13 (46%) in Group 1, 7/13 (54%) in Group 2, 9/14 (64%) in Group 3 and 9/13 (69%) in Group 4. 31/68 patients experienced side effects (e.g. taste disturbance). 11 patients did not complete the study. Analysis on an intention-to-treat basis gave similar results.

Conclusion: The dosing regimen of lansoprazole appears to be more important than the duration of therapy. Dual therapy with lansoprazole and clarithromycin is a safe and effective treatment for *Hp*.

W61

HELICOBACTER PYLORI ERADICATION THERAPY: A COMPARISON BETWEEN EITHER OMEPRAZOLE OR RANITIDINE IN COMBINATION WITH AMOXYCILLIN PLUS METRONIDAZOLE.

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Background

We have previously shown in a large series of *H. pylori* infected patients that OAM2 which is a two week course of omeprazole (40mg daily) in combination with amoxycillin (500mg TDS) plus metronidazole (400mg TDS) is better tolerated than standard triple therapy and produces a higher eradication rate especially in those patients with a metronidazole-resistant (MR) organism. Recently it has been suggested that RAM2 which is the same antibiotic combination used in conjunction with ranitidine is also an effective form of anti-helicobacter therapy.

Results

We have treated 48 HP+ve patients with RAM2 and compared them with a series of 306 HP+ve patients given OAM2. The two treatments were similarly tolerated but the eradication rate for RAM2 of 75% (36/48) was lower than that for OAM2 (90% or 274/306, $p<0.01$). In patients with metronidazole-sensitive infections both RAM2 and OAM2 gave similar eradication rates of 96% and 98% respectively but when patients' infections were metronidazole-resistant OAM2 was significantly more effective (50% and 76% respectively, $p<0.04$).

Conclusion

OAM2 is more effective than RAM2 particularly in patients with MR infection.

W63

DETERMINATION OF THE OPTIMUM DOSE OF OMEPRAZOLE IN A NEW TRIPLE THERAPY REGIMEN FOR ERADICATING HELICOBACTER PYLORI. P Moayyedi, DS Tompkins, ATR Axon. Centre for Digestive Diseases, The General Infirmary at Leeds, UK.

Introduction A simple, safe and effective regimen is required to eradicate *Helicobacter pylori*. We have reported that omeprazole 20mg bd, clarithromycin 250mg bd and tinidazole 500mg bd for one week eradicates *H.pylori* in over 90% of patients. The antibiotics in this regimen are relatively acid stable and clarithromycin solubility is increased in an acid environment. The dose of omeprazole in this regimen may therefore be important and this study was designed to investigate this further.

Methods Patients with *H.pylori* infection at endoscopy as assessed by histology, rapid urease test, microbiology and 13C urea breath test (13C-UBT) were randomised into three groups. All groups received clarithromycin 250mg bd and tinidazole 500mg bd for one week. In addition group one was prescribed omeprazole 20mg bd, group two was prescribed omeprazole 20mg od and group three received no omeprazole. Eradication was assessed by repeat 13C-UBT four weeks after treatment. Adverse events and compliance were evaluated by patient interview.

Results Sixty six patients were enrolled (mean age 49.3 years, age range 16-73, 35 males). Eradication rates were as follows: Group one 23/24 (96%), group two 20/22 (91%), group three 14/20 (70%). *H.pylori* sensitivities were available on three patients who failed to eradicate. Two were sensitive to both clarithromycin and tinidazole, one was resistant to both antibiotics. In patients who were eradicated 18/18 were sensitive to clarithromycin and 12/18 were sensitive to tinidazole. Adverse events occurred in 24% of patients. The commonest side effect was mild diarrhoea.

Conclusion Clarithromycin and tinidazole alone will eradicate *H.pylori* but efficacy is improved if omeprazole is added.

W62

A SUCCESSFUL ONE WEEK ANTIBIOTIC REGIME FOR HELICOBACTER PYLORI ERADICATION

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The optimum regime for helicobacter pylori eradication remains unclear. The aim of this study was to assess omeprazole combined with 7 days of amoxycillin and metronidazole as eradication therapy for duodenal disease.

Methods; All patients had endoscopically proven ulcer disease. *H. pylori* colonisation was confirmed by histology and rapid urease test (CLO test) at endoscopy (n=94) or by ¹⁴C urea breath test (n=10). Patients received omeprazole 40mg od for 14 days plus amoxycillin 500 mg tds and metronidazole 400mg tds for 7 days. Eradication was determined by ¹⁴C urea breath test 4 weeks after completion of treatment.

Results; 104 patients (M:F 72:32) (mean age 57.6 yrs; SE:10.7) received triple therapy in whom 85 had duodenal ulcer disease (GU 5, bleeding ulcer 9, gastritis 5). *H. pylori* was eradicated in 87 of 104 patients (84%, 95% CI: 77-91%) as determined by ¹⁴C breath test. 91% of patients completed the full course of treatment, and although 44% experienced side effects (diarrhoea 10%, metallic taste 10%, tiredness 13%) this resulted in termination of therapy in only 4% of patients. One patient developed pseudomembranous colitis (C. Difficile to in positive) within 3 days of therapy and required hospitalisation.

Conclusion; Triple therapy with omeprazole and 1 week of amoxycillin and metronidazole is effective and acceptable eradication therapy. Significant side effects remain a problem despite the short course of treatment.

W64

CLARITHROMYCIN FOR THE CURE OF HELICOBACTER PYLORI (*H pylori*) INFECTION.

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AIM of the study is to verify whether Clarithromycin is suitable for the treatment of *H pylori* infection in association with other antimicrobial and/or antsecretory drugs. **DESIGN:** prospective study with two schedules: A) 4 x 120 mg BCS plus 250 mg x 2 Clarithromycin and 250 mg x 4 Metronidazole for 14 days . B) 40 mg Omeprazole plus 250 mg x 2 Clarithromycin and 250 mg x 4 Metronidazole for 14 days. **PATIENTS AND METHODS:** 62 consecutive Hp-positive subjects (38 M; 24 F; mean age 51.7; range 27-82) as outpatients, subdivided as follows: 37 scarred Duodenal Ulcer (DU); 8 scarred Gastric Ulcer (GU); 14 Gastritis, 3 other. All patients had an endoscopically and histologically documented lesion (modified Giemsa staining). At the end of the therapy, patients were left untreated for 2 months until the endoscopy was repeated. Venous blood samples for serum Gastrin, PGA, PGC, Anti-Hp antibodies (IgG) determination were performed at each endoscopic examination. **Statistical analysis** was performed by means of Student's t test for paired data.

RESULTS: The *H pylori* cure rate were 100% (23/23) for schedule A and 92.3% (24/26) for schedule B. **Histology:** Hp-cured pts. showed a significant decrease in the activity of gastritis both in the antrum and in the body of the stomach ($p<0.0001$). Moreover, cured pts had a significant fall of PGA, PGC and IgG anti Hpylori.

(x ± DS):	Gastrin	PGA	PGC	IgG
before	71.8 ± 62.3	121.8 ± 76.9	20.3 ± 14.1	114.7 ± 110.7
after	61.7 ± 28.9	79.7 ± 37.1	7.0 ± 3.2	37.4 ± 42.0
p	n.s.	0.0004	< 0.0001	<0.0001

CONCLUSIONS: Triple therapy with Clarithromycin is very useful in curing *H pylori* infection, approaching 100% cure rate.

W65

DUODENAL ULCER RELAPSE FOLLOWING SUCCESSFUL *HELICOBACTER PYLORI* ERADICATION. PS Phull¹, D Halliday², AB Price³, MR Jacyna¹. Departments of ¹Gastroenterology, ²Nutrition & ³Histopathology, Northwick Park Hospital, Harrow, Middlesex.

It is now well recognised that most duodenal ulcers are associated with *H. pylori* infection and it has been claimed that eradication of the organism may effectively 'cure' the disease. Ulcer relapse following *H. pylori* eradication therapy is associated with unsuccessful eradication, recrudescence or reinfection with the organism. We have reviewed the data on symptoms and ulcer relapse in patients we have treated with *H. pylori* eradication therapy at Northwick Park Hospital.

Methods: A total of 86 patients had been treated with a variety of *H. pylori* eradication regimens. All patients had a diagnosis of duodenal ulceration based on recent endoscopic or barium meal findings. *H. pylori* status was confirmed by histology and/or ¹³C-urea breath test (UBT) prior to treatment. Eradication was defined as a negative UBT 4-5 weeks after completion of the treatment course. Patients were followed up at 6 monthly intervals when UBT was repeated. Repeat endoscopy and UBT were performed if there was symptomatic relapse in those patients who had eradicated *H. pylori*.

Results: 60 of the 86 patients(69.8%) eradicated *H. pylori*. The mean follow-up period was 24 months(range 12-36). 4(6.7%) of the 60 patients with negative UBT at 1 month subsequently had a symptomatic relapse: 2 within 3 months, 1 at 9 months and 1 at 36 months. Endoscopic examination revealed ulcer relapse in all 4 patients. However histology(corpus, antrum & duodenum) and UBT showed that only the 2 patients with early relapse were *H. pylori* positive. Further investigation of the 2 patients who relapsed despite successful *H. pylori* eradication revealed normal fasting serum gastrin levels. There was no history of aspirin or NSAID ingestion. Both the patients were male although only one was a smoker.

Conclusions: Duodenal ulcer relapse may rarely occur despite eradication of *H. pylori* - the multifactorial nature of this disease needs to be remembered.

W66

THE PREDICTIVE VALUE OF *HELICOBACTER PYLORI*(Hp) NEGATIVITY FOR DUODENAL ULCER(DU) RECURRENCE. AH Mohamed, J Wilkinson, RH Hunt. McMaster University Medical Centre, Hamilton, Ontario, Canada.

Hp eradication prevents DU recurrence. The course of the infection after treatment is less well documented. Our aim was to determine any relationship between Hp negativity, reinfection and DU recurrence and to determine the predictive value of Hp negativity for DU recurrence.

Methods: A fully recursive Medline search identified 28 articles reporting DU recurrence after Hp eradication between 1988 and 1993. Non English and/or dual publications were excluded. 12 papers and 10 abstracts met the following criteria: endoscopic healing of DU prior to follow up, eradication of Hp detected by histology, culture or urea breath test, and endoscopy performed at the end of follow up. **Results:**

DU RECURRENCE AFTER Hp ERADICATION					
DU recurrence at 1 year					
p/a	Rec/Hp-	%	Rec/Hp+	%	RI/Ep
p	10/254	4	132/165	80	10/31 32
±CI		6±15		74±29	31±41 10%
a	7/290	2	122/181	67	14/29 48
±CI		2±10		69±34	65±42 8%
DU recurrence after 1 year (18mo-48mo)					
p+a	1/209	0	55/74	74	7/9 78
±CI		0		81±44	55±44 7%

p=papers a=abstracts m=mean CI=95% confidence interval
Rec=recurrence RI=reinfection mo=months

Conclusion: The probability of DU recurrence if Hp- at 1 year (4±10%) is less than in patients Hp+ (71±26%)(p<0.001). Hp negativity beyond 1 year reduces recurrence to virtually 0. 8 to 10% of patients become reinfected and a DU recurrence will occur in between a 1/3 and 1/2 of these patients. If Hp negative, the probability of not developing a DU is highly significant.

W67

***HELICOBACTER PYLORI* ERADICATION Vs MAINTENANCE THERAPY FOR THE PREVENTION OF RECURRENT BLEEDING FROM DUODENAL ULCER.** C Santander, M Pérez-Miranda, A Gómez-Cedenilla, P Carpiñero, RG Grivalos, JM Pajares. Gastroenterology Department. Hospital de la Princesa. Universidad Autónoma de Madrid. Madrid. Spain.

Aim: To compare the risk of recurrent hemorrhage from ulcer in patients with duodenal ulcer (DU) disease on maintenance antisecretory agents with *Helicobacter pylori* (HP) eradication therapy.

Patients and methods: Forty consecutive patients (mean age: 56.9; M / F: 28 / 12) presenting with a first episode of endoscopy proven bleeding from DU were included. Those with a history of NSAIDs, steroids or antibiotics intake in the eight weeks prior to presentation were excluded.

HP infection was diagnosed when at least two of the following tests were positive: 1/ histologic examination of antral biopsy specimens in frozen tissue sections on H-E and/or Giemsa. 2/ rapid urease test (Jatrox) on antral samples. 3/ IgG anti HP serology (Helico G ELISA) with an antibody titre over 12 U/ml.

After the acute phase of bleeding, patients were randomly allocated into two treatment groups : 1/ Eradication therapy (ET), 20 patients, in one of the following two regimes, a) Amoxicillin 500 mg tid for 10 days + Omeprazole 20 mg bid for 30 days, or b) Amoxicillin 500 mg tid for 10 days + Metronidazole 500 mg tid for 10 days + Colloidal Bismuth Subcitrate 300 mg bid for 30 days. If HP infection recurred, a second course of ET on the alternative regime was tried. 2/ Long-term maintenance treatment (MT), 20 patients randomly allocated to either Omeprazole 20 mg once a day or ranitidine 150 mg once a day for one year.

Follow-up included bimonthly clinical assessment and upper endoscopy every three months. Mean follow up: ET = 2.26 years; MT = 1 year

Results:

	n	HP+ve (after ET)	DU relapse	Rebleeding
ET 1st course				
a)	11	5/11	1/11	0/11
b)	9	2/9	0/9	0/9
2nd course				
a)	2	0/2	0/2	0/2
b)	5	0/5	0/5	0/5
MT (before MT)				
Omeprazole	6	3/6	2/6	1/6
Ranitidine	14	14/14	4/14	2/14

Conclusions: HP eradication therapy is more effective in preventing recurrent bleeding from DU than long-term maintenance treatment.

W68

GLUCOSE AND UREA: SOURCES OF CARBON FOR *H. PYLORI* ? S Khulusi, HA Ahmed, P Patel, MA Mendall and TC Northfield. Department of Medicine, St. George's Hospital Medical School, London.

Introduction: Urea and glucose are present in high concentrations in the gastric mucosa and juice. Both are potential sources of carbon for *H. pylori*. Glucose is oxidised by the organism but its conversion into structural components has not been demonstrated. Large quantities of urease are produced by *H. pylori* but a metabolic role for the products of urea hydrolysis has not been shown. We aimed to determine whether *H. pylori* is able to utilise carbon obtained from glucose or urea hydrolysis, for structural or metabolic purposes.

Method: *H. pylori* was incubated in Brucella broth with 10% horse serum and antibiotic supplements at 37°C under microaerophilic conditions. ¹⁴C urea (2 and 10mM) and ¹⁴C glucose (2 and 10mM) were added to separate cultures containing approximately 5x10⁷ organisms/ml in mid-log growth and incubated for 48hrs. Optical density changes of cultures at 540nm were used to assess numbers of organisms. Optical density was shown to be closely related to viable count performed on chocolate agar plates (r=0.94, p<0.001). Morphology of the organism was assessed by light and by electron microscopy and urea hydrolysis by a photometric process employing the Berthelot reaction. *H. pylori* were separated from the culture medium by centrifugation and washing at 24 and 48hrs. Incorporation of ¹⁴C label was determined by scintillation counting of the separated *H. pylori*. Folch extraction was used to isolate *H. pylori* lipid, which was then separated on thin layer chromatography. Fatty acid and phospholipid bands on chromatograms were visualised by iodine staining and quantified by scintillation counting.

Results: Glucose and urea at the concentrations used did not affect *H. pylori* growth compared to control growth. ¹⁴C label from glucose was incorporated into *H. pylori* cell mass and was detected in the fatty acid (0.13 umol of glucose/g) and phospholipid fractions (0.19 umol of glucose/g) of the organism. However there was no incorporation of the ¹⁴C label from urea into *H. pylori* cell mass.

Conclusion: Glucose is utilised by *H. pylori* as a source of carbon and can be used for the biosynthesis of fatty acids and phospholipids. Urea hydrolysis, however, does not provide a source of carbon for the organism. Further characterisation of *H. pylori* carbon metabolism may be important in the development of therapeutic agents.

W69

INCREASED INTERLEUKIN-8 mRNA IN GASTRIC EPITHELIAL CELLS OF PATIENTS WITH *Helicobacter pylori* INFECTION: DETECTION USING A NOVEL QUANTITATIVE CHEMILUMINESCENT ASSAY FOR PCR PRODUCTS.

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Introduction: Persistent active antral inflammation with *Helicobacter pylori* infection is associated with increased mucosal levels of neutrophil chemoattractant interleukin (IL)-8. To test whether *H. pylori* infection is associated with increased epithelial cell IL-8 mRNA levels, we devised and used a novel quantitative chemiluminescent assay for PCR products.

Method: Epithelial cells were digested from single antral biopsies from 16 *H. pylori* infected and 16 control patients by 30 minute collagenase digestion and the level of non-epithelial contamination was confirmed to be low by cytospin analysis. Extracted RNA (RNAzol B) was reverse transcribed (RT) and IL-8 and β actin cDNA were amplified by PCR (31 cycles) using in house primers. PCR products were dot-blotted onto nylon membranes, uv crosslinked, hybridized with alkaline phosphatase labelled probes (16-mers), and quantitated using a chemiluminescent substrate (LumigenTMPPD) by counting the membrane in a microplate scintillation counter.

Results: The assay was quantitative between 10pg(50 attomoles) and 3ng(15 femtomoles) of product. 31 cycles of PCR gave quantitative results between 0.001 and 1fg of substrate.

IL-8 RT-PCR product from *H. pylori* infected patients was 1354 (504-2200)pg/ μ l (median (IQR)) compared to 193(29-400)pg/ μ l from control patients (p<0.002).

The ratio IL-8(pg)/actin(ng) RT-PCR products for *H.p.* infected patients was 52 (13-75) compared to 11 (4-29) for control patients (p<0.05).

Conclusion: *H. pylori* infection is associated with increased IL-8 mRNA levels in epithelial cell preparations. This is further evidence that increased IL-8 production by epithelial cells may be instrumental in initiating active antral gastritis.

W71

HELICOBACTER PYLORI GROWTH IS INHIBITED BY UPTAKE AND INCORPORATION OF LINOLEIC ACID.

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Introduction: The prevalence of duodenal ulcer disease is inversely related to dietary unsaturated fatty acids (FA). We have shown that unsaturated FA inhibit the growth of *H. pylori* in-vitro. However, the mechanism of inhibition is unknown. We aimed to determine whether an inhibitory FA, linoleic acid (LA) and a less inhibitory FA, oleic acid (OA) are incorporated into *H. pylori* and whether this incorporation is related to the degree of growth inhibition.

Methods: *H. pylori* was incubated in Brucella broth with 10% horse serum and selective antibiotics at 37°C under microaerophilic conditions. ¹⁴C-LA and ¹⁴C-OA (2.0 and 5.0mM) were added to separate cultures and incubated for 48hrs. Optical density changes of cultures at 540nm were used to assess numbers of organisms. Optical density was shown to be closely related to viable count performed on chocolate agar plates (r=0.94, p<0.001). *H. pylori* were separated from the culture medium by centrifugation and washing at 24 and 48hrs. Incorporation of radio labelled FA was determined by scintillation counting of the separated *H. pylori*. Folch extraction was used to isolate *H. pylori* lipid, which was then separated on thin layer chromatography. Free FA and phospholipid bands on chromatograms were visualised by iodine staining and quantified by scintillation counting.

Results: Table shows (mean $\pm$ SEM) growth rate of *H. pylori* in the presence of LA and OA, and the incorporation of these fatty acids (umol of fatty acid/g of *H. pylori* protein) into *H. pylori* cell mass and phospholipids after 24 and 48hrs incubation:

Fatty Acid		Growth rate (% of control)		Incorporation of fatty acid into <i>H. pylori</i> : cell mass				phospholipids	
		2mM	5mM	2mM	5mM	2mM	5mM	2mM	5mM
LA	24hr	34 $\pm$ 7	7 $\pm$ 3	10.9 $\pm$ 2.0	36.8 $\pm$ 7.8	2.2	1.1		
	48hr	8 $\pm$ 2	2 $\pm$ 2	10.5 $\pm$ 1.9	24.8 $\pm$ 6.0	3.1	1.6		
OA	24hr	96 $\pm$ 10	69 $\pm$ 11	3.1 $\pm$ 1.0	9.5 $\pm$ 2.2	0.1	0.1		
	48hr	76 $\pm$ 8	39 $\pm$ 4	6.8 $\pm$ 0.4	19.6 $\pm$ 3.0	0.1	0.2		

At the concentrations tested, LA produced greater inhibition of *H. pylori* growth than OA as well as greater incorporation into *H. pylori* cell mass and phospholipids.

Conclusion: The inhibitory effect of LA on *H. pylori* growth in vitro is associated with incorporation and accumulation of the FA into the organism. This finding may have therapeutic implications.

W70

HISTOLOGY, IGG, IGA, IGM TO HELICOBACTER PYLORI (HP), SERUM PEPSINOGEN I (PGI) AND GASTRIN (G) IN ASYMPTOMATIC BLOOD DONORS (BD). D Vaira, M Miglioli, M Menegatti, J Holton¹, P Mule², G Oderda², G Biasco, P Azzarone, C Ricci, M Lombardi, F Altare², R Conte, C Ainley³, L Barbara. 1st Medical Clinic, University of Bologna, 2 Dept of Paediatric, Turin Italy, 1 Dept of Microbiology, University College London, 3 London Hospital Medical College, London, UK.

We previously reported the serum levels of IgG, IgA, IgM to HP and Pgl and G in 1010 BD and we now report their serum levels in relation to histology. 359 of the 1010 BD consented to endoscopy.

Aim: To evaluate serological parameters of HP infection compared to histology. **Methods:** IgG, IgA, IgM were assessed by ELISA (Absorbance Index >0.3 positive) and Pgl (ug/ml) and G (pg/ml) by RIA. By IgG levels 422/1010 were HP+ve. Endoscopy with biopsies was carried on in 298 HP+ve (M/F: 173/125; age range 18-65, mean 45 yrs) and 61 HP-ve (M/F: 46/15; age range 18-65, mean 42 yrs). At endoscopy IgG were reassessed. **Results:** Table 1 shows the mean value of the parameters in HP+ve and HP-ve according to IgG.

	IgG	IgA	IgM	Pgl	G
sero+ve(n=422)	0.9	0.45	0.6	86	29
sero-ve(n=577)	0.19	0.24	0.66	61	25

Table 2 shows the mean IgG at repeat assessment with the original IgA, IgM, Pgl and G levels in the endoscoped BD. No differences were found between the total 1010 BD population and the 359 who consented to endoscopy. Mean IgA levels were higher in IgG+ve (P<0.01). Serum G was unrelated to IgG levels.

	IgG	IgA	IgM	Pgl	G
Endoscoped					
sero+ve(n=298)	0.7	0.44	0.57	85	29
sero-ve(n=61)	0.2	0.22	0.62	78	26

Table 3 shows the number of BD positive for HP by each test. Initial IgG Giemsa Repeat IgA IgM Pgl

	+ve	+ve	+ve	+ve	+ve
IgG +ve(298)	274	280	146	204	138
IgG-ve(61)	2	2	10	36	31

Conclusion: 1. Serum IgG are confirmed as the most reliable serologic test with little variation at repeat assessment; 2. Mean IgA levels, but not IgM, Pgl and G were higher in HP+ve by IgG titre.

W72

H. PYLORI IMPAIRS ACID-INHIBITION OF PEPTONE-STIMULATED ACID SECRETION. Calam J, Kovacs TOG, Sytnik B, Walsh JH. UCLA School of Medicine, Los Angeles.

It was observed in the 1970s that a low intra-gastric pH inhibits meal-stimulated gastrin release and acid secretion less in duodenal ulcer patients than in controls. The present study asked whether this is due to *H. pylori* infection.

Methods: Asymptomatic non-ulcer volunteers were studied; 9 uninfected; mean age 33 years, and 8 infected; mean age 37 years. Acid secretion was measured by intra-gastric titration for 3 hours, during gastric distension with 8% peptone at pH 7.0 and pH 2.5 on separate occasions.

Results: The mean rates of acid secretion were similar at pH 7 during the 1st, 2nd and 3rd hours in uninfected and infected volunteers: 16.7 - 20.3 and 15.8 - 19.8 mmol/h respectively. In uninfected subjects, the mean rate of acid secretion at pH 2.5 was inhibited to <20% of the rate at pH 7 during all of the 3 hours: hour 1 to 16%, hour 2 to 16%, hour 3 to 19%. In infected subjects the mean rate of acid secretion was inhibited similarly during the first hour to 22%, but significantly (P<0.05) less during the second and third hours; to 52% and 56% of acid secretion at pH 7 respectively. When the intra-gastric pH was 2.5, mean meal-stimulated acid secretion rates during the 2nd and 3rd hours were 3.1 and 2.8 times higher in infected subjects than in uninfected subjects. Plasma gastrin was significantly higher, and was also inhibited less by the low pH, during all of the 3 hours in infected subjects.

Conclusion: *H. pylori* causes a failure of acid-inhibition of meal-stimulated acid secretion. This is consistent with impaired expression of somatostatin and may contribute to the ulcerogenic effect of this infection by allowing acid secretion to persist in the late postprandial period when the intragastric pH has fallen.

W73

SURVIVAL OF *HELICOBACTER PYLORI* IN ANIMAL MODELS

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Helicobacter pylori (*H. pylori*) does not survive in the rodent stomach. *Helicobacter muridarum* occupies the rodent ileum and can survive in the stomach of a rodent with gastro-duodenal reflux. The study examined whether *H. pylori* could colonise the PVG (heterozygote and nude) rat and the Wistar rat with a surgical gastro-jejunostomy.

20 PVG nude and 20 heterozygote rats were given 10^6 of freshly cultured *H. pylori* by gavage. 20 Wistar rats underwent a gastro-jejunostomy and at a minimum of 4 months post-operatively 14 were given *H. Pylori*. 2 animals from each group were sacrificed at weekly intervals and their stomachs examined by histology, urease test and polymerase chain reaction (PCR) using two published primer sequences, one from the 16S RNA gene and one from a gene encoding urease (*UreC*). A positive (pure culture of *H. pylori*) and negative control was included in each PCR reaction.

RESULTS

No *Helicobacter*-like organisms were demonstrable histologically. All animals exhibited delayed CLO[®] test positivity (12-24 hours) presumably due to their gastric flora visible on histology. PCR demonstrated that in the nude PVG rat organisms were present in the glandular stomach for 4 weeks following administration. No positive results were obtained from the heterozygote group. The Wistar rats showed histological evidence of reflux gastritis. *H. pylori* was demonstrated in the glandular stomach for 4 weeks, the region of the gastro-jejunostomy for 6 weeks and the proximal duodenum for 4 weeks following dosing. The gastro-jejunostomy animals which did not receive *H. pylori* were negative.

CONCLUSION

H. pylori survives in the nude rat with a defective cellular immune system, indicating that this part of the immune response may be involved in host resistance to *H. pylori*. Changes in the gastric milieu due to a gastro-jejunostomy provide conditions in which *H. pylori* survive. *H. pylori* may be more resilient than its specificity for the human gastric mucus indicates.

Small bowel/nutrition W75-W89

W75

¹¹¹IN CHLORIDE-TRANSFERRIN SCANNING FOR DETECTION AND QUANTIFICATION OF PROTEIN LOSING ENTEROPATHY MS CARPANI de KASKI, AM PETERS, DM GLASS, HJF HODGSON

Current techniques for assessing of protein loss through the gastrointestinal tract, although adequate for quantification, are relatively ineffective for localization of protein loss. We assessed the usefulness of ¹¹¹In chloride-transferrin for the imaging and quantification of protein loss in patients. ¹¹¹In chloride becomes transferrin-bound, both *in vivo* and *in vitro*, and has a long half life that allows quantification of its gastrointestinal loss. Fifteen studies in 13 patients with hypoalbuminaemia and suspicion of protein losing enteropathy were performed. In each patient, autologous plasma was incubated with 15 MBq of ¹¹¹In chloride and re-injected into the patient after 15-20 minutes. Early and late images of anterior abdominal views were taken with a gamma camera to localize the site of protein loss. Whole body excretion (WBE) was calculated from whole body counting with an uncollimated gamma camera at 3 hrs and 5 days after of injection of isotope. A gastrointestinal site of protein loss was identified in 10 of the 15 studies (8 patients) - 5 small bowel; 5 large bowel. In these patients, the amount of protein loss, as assessed by WBE, ranged from 16% to 34% of the injected dose (normal value <10%). In the remaining 5 patients ¹¹¹In chloride-transferrin imaging failed to localize a gastrointestinal site of protein loss, and WBE was less than 10%. We conclude that the combined use of ¹¹¹In chloride-transferrin imaging and the WBE technique is a useful method for the detection and quantification of protein loss through the gastrointestinal tract.

W74

AN ANIMAL MODEL OF *HELICOBACTER PYLORI* INFECTION

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An ideal animal model of *Helicobacter pylori* infection has not been described. Most animal models such as the Japanese monkey, the gnotobiotic piglet and other primates are not suitable for large scale experiments. There has been one successful colonisation of the nude and athymic mouse using large quantities of fresh cultures but this is not readily reproducible. An acute gastritis, similar to that in man is seen when *Helicobacter felis* (*H. felis*) is given to the germ free mouse. When the germ free rat is used, only a chronic gastritis is produced.

This study has examined the effect of *H. felis* on the PVG nude rat. 12 animals were given 2 mls of 10^6 per ml of *H. felis*. 2 animals were sacrificed at weekly intervals for 4 weeks and then at 8 and 10 weeks and their stomachs examined histologically and by urease testing. Control animals were given broth only.

RESULTS:

The animals were successfully colonised with *H. felis* as determined by CLO[®] test and histology. For the first 8 weeks the infection was confined to the gastric antrum with organisms occupying the gastric crypts. For the first 4 weeks there was a gradual increase in the degree of inflammation in the antrum with no obvious changes within the remainder of the glandular part of the stomach. The inflammatory response was predominately chronic in nature with a large number of eosinophils and frequent lymphoid follicles. At 8 weeks the inflammatory response appeared to be regressing but at 10 weeks organisms were for the first time visible within the glandular portion of the stomach with an early inflammatory response.

CONCLUSION

The pattern of inflammation produced in this animal model closely resembles that encountered in man and will be a useful model to study the pathogenicity of gastric spiral organisms and the mucosal changes they produce.

W76

INULIN IS A BETTER PROBE THAN LACTULOSE FOR THE MEASUREMENT OF ORO-CAECAL TRANSIT TIME

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Lactulose is widely used to measure the oro-caecal transit time by the H₂ breath test, but its osmotic effect may artifactually shorten the transit time. Inulin, an undigestible oligosaccharide, produces a H₂ peak when confronted with colonic bacteria; it has a lower osmotic effect than lactulose and should ideally cause a smaller derangement of transit. Our aim was to compare the breath H₂ profiles after 5 or 10 g of lactulose (L) or inulin (I) taken with an 800 Kcal solid meal (15% from proteins, 45% fats, 40% carbohydrates) in 8 normal subjects. The oro-caecal transit time was calculated at the time of 10 ppm increase of expired H₂, ignoring early peaks. The ultrasonographic gastric emptying was also evaluated to assess its possible role in the results. Mean $\pm$ SEM are shown. The ANOVA for repeated measurements and the paired Student's t test were used for the analysis. **RESULTS.** The baseline H₂ values after inulin were low and stable, and the late peak easily traceable; after lactulose, a marked fluctuation of basal values was found, making the identification of the start of the peak rather subjective. The oro-caecal transit times were markedly different after the four sugar probes (I 5g: 232 $\pm$ 22.5 min; I 10g: 276 $\pm$ 26.0 min; L 5g: 219 $\pm$ 12.0; L 10g: 137 $\pm$ 16.9 min; p<0.001, RM-ANOVA). Both doses of lactulose reduced the transit time, the difference being statistically significant for L10g vs all other groups. L10g induced a slight but consistent delay of gastric emptying (I 5g: 202 $\pm$ 15.6min; I 10g: 192.8 $\pm$ 15.2min; L 5g: 200 $\pm$ 17.4; L 10g: 215.9 $\pm$ 20.8min; p<0.001, RM-ANOVA; p=0.05 L5g vs L10g). **CONCLUSIONS:** inulin produces a more reliable measurement of oro-caecal transit time than lactulose. Inulin does not cause the artifactual onset of early hydrogen peaks, and does not alter the gastric emptying rate. It is therefore a better probe than lactulose for gastrointestinal motility studies.

W77

PROBLEMS WITH POLYETHYLENE GLYCOL (PEG) AS A MARKER OF SMALL INTESTINAL PERMEABILITY

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Although PEG is widely used as a marker of small intestinal permeability (SIP) the permeation of PEG in vivo displays anomalies compared to sugar probes of comparable size: i) PEG 400 (ave MW) is absorbed and excreted about 100 times more avidly than lactulose (MW 342); ii) Recovery of the lowest molecular weight polymers is very variable. We investigated the permeation of PEG in vivo using a combined probe consisting of PEG (MW 280-1000) with lactulose (L) and mannitol (M). To investigate the effects of volume of distribution (Vd) and renal handling, timed tests were performed both under fasted and fluid-hydrated conditions in the same subjects. After overnight fast 6 normal subjects ingested M (2.5g), L (10g), PEG 400 (0.5g), 600 (3g), 900 (5g) and 1000 (0.5g) dissolved in 100ml water. Fluid-hydrated subjects ingested 100ml water 1 hour before and at hourly intervals after ingestion of the probe mixture. All urine was collected in hourly aliquots for 6 hours. HPLC was used for probe analysis using pulsed amperometric detection for sugars and refractive index detection for PEG. Results were expressed as hourly L/M excretion ratios (LMER) and PEG excretion as percentage of administered dose. Significantly more PEG was excreted in the fluid-hydrated compared to the fasted state (mean AUC 1.51 compared to 1.08 $p < 0.01$). Greater amounts of low compared to high MW PEG were seen at 5h compared to 2h in each experiment. There were no differences in L, M excretion nor LMER between fasted and fluid-hydrated tests. LMER did not change from hour 1-6. We conclude that PEGs may undergo renal tubular absorption and have larger Vd than sugars. This makes them unsuitable as markers of small intestinal permeability.

W79

FASTING AND POST-PRANDIAL POLYAMINE CONCENTRATIONS IN THE HUMAN SMALL BOWEL

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BACKGROUND: The polyamines (PAs), putrescine, spermidine and spermine and their acetylated derivatives, influence normal, adaptive and neoplastic growth in the intestinal mucosa. Within the enterocyte, their concentrations are regulated, not only by enzymes controlling their synthesis and degradation, but also by PA transport from the circulation (across the basolateral membrane) and the lumen (across the apical membrane). In turn, luminal PAs may be: (i) ingested with food, (ii) synthesised by intestinal bacteria, and (iii) present in pancreaticobiliary secretions. However, there are no data about luminal PA concentrations in man. **METHODS:** Therefore, in 5 healthy volunteers we intubated the duodenum and jejunum, and measured luminal PA samples aspirated before, and at 15 min intervals for 2h after, giving 200ml of a PA-rich liquid test "meal" (commercial orange juice) containing 2.5g/100ml polyethylene glycol (PEG 4000) as a dilution marker. The aspirates were extracted with 0.2M perchloric acid and their PA concentrations measured by HPLC. **RESULTS:** In all the fasting duodenal and jejunal aspirates, there were low levels of putrescine (14.9 ± 3.4 , $16.4 \pm 4.3 \mu\text{M}$), spermidine (3.2 ± 1.1 , $5.4 \pm 1.6 \mu\text{M}$), spermine (4.0 ± 4.2 , $1.7 \pm 4.2 \mu\text{M}$), N1-acetylspermine (11.8 ± 2.8 , $7.4 \pm 2.8 \mu\text{M}$), and the bacterially-derived cadaverine (6.1 ± 1.7 , $6.2 \pm 1.7 \mu\text{M}$) and acetylcadaverine (4.9 ± 2.3 , $5.2 \pm 2.3 \mu\text{M}$). Traces of N1- and N8-acetylspermidine were found in one duodenal and one jejunal sample. The orange juice contained putrescine ($871 \pm 44.6 \mu\text{M}$) and spermidine ($31.3 \pm 3.5 \mu\text{M}$) but there were no other PAs present. The peak duodenal and jejunal PA concentrations were seen 30 min after drinking orange juice (putrescine $385 \pm 75.1 \mu\text{M}$ and $279 \pm 74.2 \mu\text{M}$ respectively), at a time when the PEG concentrations in the duodenum and jejunum had fallen to 1.33 and 0.98g/100ml respectively, indicating marked meal dilution. Thereafter, putrescine concentrations fell to half their peak values at 60 min and to levels comparable to those seen in the fasting aspirates, by 120 min. **INTERPRETATION:** These non-steady state studies do not distinguish between meal dilution, bolus passage and net PA transport but they do provide the first data on fasting and post-prandial intestinal luminal PA concentrations in man - essential information for subsequent studies of PA absorption at physiological concentrations, using a steady-state perfusion technique.

W78

ORIGINS OF INTESTINAL LUMINAL POLYAMINES IN MAN

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BACKGROUND: The polyamines (PAs), putrescine, spermidine, spermine, and their acetylated derivatives, are found in all mammalian cells, act as second messengers and are essential for cell division and growth. Exogenous PAs are synthesised from ornithine although enterocytes can also absorb "exogenous" PAs from the circulation and the intestinal lumen, but little is known about the origins of luminal PAs, from (i) food, (ii) intestinal bacteria and (iii) bile (PAs may have an enterohepatic circulation). **METHODS:** We, therefore, extracted PAs with perchloric acid and measured their concentrations by HPLC in: (i) duplicate samples of selected fast foods (hamburgers, cheese burgers, fish fillets, orange and grapefruit juices and boiled prawns), (ii) concentrated (bile acids $> 100\text{mM}$) fresh gallbladder bile obtained by ultrasound-guided fine needle puncture (part of a separate study; $n=12$) and (iii) duodenal aspirates, obtained at endoscopy, from 7 patients with small bowel bacterial overgrowth (SBBO: arbitrarily defined as $> 1 \times 10^5$ colony forming units/ml of aspirate.) **RESULTS:** Of the convenience foods, the highest PA concentrations were found in the fruit juices (putrescine $228\text{--}757\text{nmol/ml}$ and cadaverine 36nmol/ml) with lesser amounts in the burgers (spermine $9\text{--}51\text{nmol/g}$ and spermidine $15\text{--}33\text{nmol/g}$). In duodenal aspirates from the 7 patients with SBBO, the highest PA concentration was the bacterially-derived acetylcadaverine ($37 \mu\text{M}$) followed by putrescine ($7.1 \mu\text{M}$), spermine ($6.0 \mu\text{M}$), cadaverine ($5.1 \mu\text{M}$) and spermidine ($4.4 \mu\text{M}$). N1-acetylspermine ($29 \mu\text{M}$) was found in one individual and N8-acetylspermidine ($1.4 \mu\text{M}$) in another. Of the PAs in gallbladder bile, only spermine ($2.4 \pm \text{SEM } 0.7 \mu\text{M}$) and spermidine ($1.5 \pm 0.2 \mu\text{M}$) were found in all 12 samples although trace amounts ($< 2.2 \mu\text{M}$) of putrescine and cadaverine were found in 3. **SUMMARY/INTERPRETATION:** These results suggest that some foods have high PA concentrations and are likely to contribute to the luminal PA pool. However, even when concentrated, gallbladder bile has negligible amounts of PAs so that, after 5-20 fold dilution in the intestine, bile is an insignificant contributor to luminal PAs. Finally, bacteria may be a source of luminal PAs but the concentrations are low - at least in the upper small bowel.

W80

SMALL BOWEL FLORA IN POTENTIAL SMALL BOWEL TRANSPLANT DONORS

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Small bowel transplantation is developing as a treatment for intestinal failure. There is concern that donor small bowel may be a potential source of infection in the recipient during the early post-transplant period. The use of a selective decontamination regime (SDD) of the donor small bowel has been proposed as a means of reducing postoperative infective complications.

This study qualitatively assessed the small bowel aerobic microflora and looked for evidence of bacterial translocation. In 20 multi-organ donors a standard liver and kidney retrieval technique was performed with administration of intravenous Cefotaxime 2 g, Gentamicin 160 mg and Benzylpenicillin 2 U. Ileal lymph nodes and bacteriological samples from the duodenum, jejunum and ileum were taken for microbiological study. Details regarding donor age, length of ITU stay, prior antibiotic treatment, anti-ulcer therapy and clinical evidence of sepsis were recorded.

Bacteria were isolated from the small bowel contents of 10 donors (50%) and cultured from ileal lymph nodes of 4 donors (20%). Yeasts were isolated from the stomach (70%) and duodenum (65%), but not from lymph nodes. No risk factors were identified for the presence of aerobic bacteria in small bowel lumen or ileal lymph nodes.

Conclusions from this study are that the commonest intraluminal microflora in multi-organ donors were yeasts and that bacterial translocation to ileal lymph nodes was present in 20%. This data would support the use of enteral antifungal agents and systemic antibiotics in potential small bowel donors and recipients, but not the use of SDD in donors. Avoiding the antibacterial components of SDD regimes would reduce the potential risk of bacterial resistance and superinfection by organisms such as Enterococci.

W81

INTESTINAL BLOOD FLOW DISTRIBUTION IN PORTAL HYPERTENSION

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While portal hypertensive gastropathy is now recognised as a clinical entity, recent reports suggest that pathological changes in portal hypertension also extend to the small and large bowel. Experimentally, portal hypertension is associated with increased total intestinal blood flow, but it is not known whether this masks redistribution of blood flow leading to regional or focal hypoperfusion. Experiments were performed in anaesthetised rats 14 days after partial portal vein ligation (PVL, n=8) or sham-operation (SO, n=8). Using ¹⁴C-iodoantipyrine autoradiography, regional intestinal blood flow was measured in luminal and basal mucosa and muscularis externa (Musc) in the proximal (PSB), middle (MSB) and distal (DSB) thirds of small bowel, and in mid-colon. Results (expressed as mean ± SE): PVL rats had increased portal venous pressure (11.9±0.6 vs 9.1±0.2mmHg) and portasystemic shunting (intraportal microspheres: 63±13 vs 0.8±0.1%) relative to SO controls. The table shows regional intestinal blood flow in ml/100g/min.

	SO			PVL		
	Luminal	Basal	Musc	Luminal	Basal	Musc
PSB	112±5	111±10	72±6	150±15*	147±17	94±11
MSB	71±5	71±5	53±4	102±9*	97±10*	71±7
DSB	50±5	51±5	42±4	76±8*	74±7*	59±4*
Colon	50±3	48±3	46±2	63±7	68±6*	60±5*

Luminal, Basal=mucosal regions; *p<0.05, PVL vs SO, Student's t test.

Blood flow was significantly increased in PVL animals in most regions without evidence of substantial redistribution. We conclude that portal hypertension is not associated with regional or focal intestinal hypoperfusion in this model.

W83

ANGIOTENSIN CONVERTING ENZYME ACTIVITY IN STOOLS OF HEALTHY SUBJECTS AND PATIENTS WITH CELIAC DISEASE.
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Several studies have been performed on the biochemical and physiopathological properties of angiotensin converting enzyme (ACE). ACE occurs in three types of cells: endothelial, epithelial and neuroepithelial. ACE activity is present in plasma, in urine and in vascular endothelium. High levels of ACE are found in the brush border of human small intestine. The aim of this study was to evaluate the ACE activity in human stools. **Subjects.** Fifteen healthy subjects (HS) (8 M, 7 F; age range 6-56 yrs), 16 patients with celiac disease (CD) (10 M, 6 F; age range 14-58 yrs) and 12 patients with CD after a gluten-free diet (CD-GFD) (4 M, 8 F; age range 15-53 yrs) where enrolled in the study. **Method.** The fecal ACE activity was measured in all groups. Fecal samples were kept at -20 °C for a subsequent test. A 2 gr aliquot of the homogenized 24 hours stools was diluted 1:4 in saline and spun at 1500-3000 g for 60 min. Fecal ACE activity was measured using 20 ul of the supernatant and expressed as nmol/100 grams per stool weight. For the statistical analysis, the Student's test for paired and unpaired samples were used as appropriate. **Results.** In HS, fecal ACE activity was 25.4±15.7 (mean±SD). In patients with CD, ACE activity was significantly higher (122.7±103) than in HS (p<0.03) except those with CD on GFD (31.8±10) (p=0.13). **In Conclusion.** we have demonstrated ACE-activity in human stools. ACE activity of stools most probably derives only from microvilli of intestinal mucosa thus suggesting the potential usefulness of ACE determination as an index of enterocyte damage.

W82

ENHANCED INTESTINAL IRON TRANSFER IN 2-3 DAY STREPTOZOTOCIN-DIABETIC RATS.

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The regulation of iron absorption across the enterocyte remains poorly understood. One possible factor is the driving force provided by brush border potential difference (V_{bb}). V_{bb} has been shown to affect absorption of glucose and amino acids. Previously we have demonstrated hyperpolarization of the brush border membrane in a model of increased iron absorption. We have also found increased iron absorption in overnight fasted rats, a condition known to increase V_{bb}. Hyperpolarization also occurs in streptozotocin induced diabetes of 4-6 weeks duration. Despite mucosal hypertrophy and increased V_{bb} iron transfer to blood is reduced. At this stage many of the complications of diabetes are evident, notably weight loss and cataract formation. In this study we measured iron transfer in early diabetics (1-3 day) where V_{bb} is increased but the other changes have not yet occurred. Sprague Dawley rats (250-300g) were treated with Streptozotocin (65 mg/kg) or citrate by tail vein injection. Iron transfer to blood from the duodenal lumen was measured (Gut suppl). Diabetics (2-3 day duration) transfer significantly more iron than controls (Table 1) but no change was seen in 1 day diabetics.

Table 1. *In vivo* transfer of ⁵⁹Fe³⁺ from duodenal loops to blood. Results (percentage of the initial luminal counts per ml of blood) are given as mean ± s.e.m.(n). *p<0.005, †p<0.01, ‡p<0.05.

Time (min):	5	10	15	20	30
Control(6)	0.3±0.1	0.5±0.2	0.9±0.3	1.0±0.3	1.3±0.3
Diabetic(4)	0.6±0.2†	1.2±0.4†	1.7±0.4*	2.0±0.4*	2.2±0.4*

This lack of an early response could be related to residual toxicity of streptozotocin. The increased absorption at two and three days could be secondary to hyperpolarization of the brush border.

W84

IN VITRO COELIAC TOXICITY OF GLUTEN PEPTIDES ASSESSED BY ORGAN CULTURE

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The precise nature of the toxic epitope(s) which exacerbates coeliac disease remains unknown. We have used an organ culture system to investigate the in vitro toxicity of three oligopeptides corresponding to amino acids 31-49 (peptide A), 202-220 (peptide B) and 3-21 (peptide C) of A-gliadin. Frazer's Fraction III (FFIII) and ovalbumin were used as controls. Jejunal biopsies were obtained from eight treated coeliac patients, seven untreated coeliac patients and six normal controls and cultured for 18 hours. A significant reduction in mean enterocyte cell height (ECH) was observed with peptide A and FFIII in both treated (p = 0.01 and 0.02, respectively) and untreated (p = 0.03 and 0.01) coeliac patients when compared with tissue incubated with organ culture medium alone. No significant changes in ECH were noted in any of the patient groups in tissue incubated with peptide B, peptide C or ovalbumin, when compared to those with organ culture medium alone. These results suggest that peptide A is toxic in vitro to the jejunal mucosa of both treated and untreated coeliac patients, correlating with recent findings that this peptide exacerbates coeliac disease in vivo.

W85

INCREASED BLOOD LEVELS OF 5-HYDROXYTRYPTAMINE IN COELIAC DISEASE.

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5-hydroxytryptamine (5-HT) is produced by enterochromaffin cells in a number of organs, including small bowel. These cells are increased in number in the flat duodenal mucosa. Intestinal tissue concentration of 5-HT is also increased in coeliac disease. Abnormalities of 5-HT metabolism can account for a number of symptoms and signs, including diarrhoea.

Fourteen patients with untreated coeliac disease (5 males, median age 45 years, range 18-79), 17 patients with treated coeliac disease (7 males, median age 51, range 26-68, median time on a gluten free diet 16 months, range 6-69) and 22 healthy volunteers age and sex matched with patients took part in the study.

Five mls of blood were taken from each fasted patient. Blood levels of 5-HT, after deproteinization in butanol, extraction in heptane-HCl and treatment with ortho-phthalaldehyde for fluorophore production, were determined, in double, using a spectrofluorimetric method. 5-HT blood levels were significantly higher in patients with untreated coeliac disease (median 11 nmol/ml, range 5-17) compared both to patients with treated coeliac disease (6, 3-9, $p < 0.0001$) and healthy volunteers (6.8, 5.4-9.2, $p < 0.0001$). Although 5-HT blood levels in patients with treated coeliac disease were comprised within the range found in healthy volunteers, they were significantly higher compared to healthy volunteers ($p < 0.05$). In patients with coeliac disease, a significant inverse correlation was found between 5-HT blood levels and duration of gluten free diet ($r = -0.58$, $p < 0.001$).

These data suggest that: a) in coeliac disease there is an increased production of 5-HT; b) 5-HT levels are strictly related to gluten intake; c) 5-HT may have a role in inducing symptoms in patients with coeliac disease.

W87

MEASUREMENT OF DUODENAL MUCOSAL PROTEIN SYNTHESIS IN PATIENTS WITH COELIAC DISEASE

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Aims: We have applied a stable-isotope tracer amino acid method to measure the rate of protein synthesis in distal duodenal mucosa in patients with coeliac disease (CD). 8 patients with histologically confirmed CD were studied and the results compared with those from a group of normal control subjects (C). **Methods:** Primed intravenous (iv) and intragastric (ig) infusion of [$1-^{13}C$] leucine and [$1-^{13}C$] valine were administered after an overnight fast. Blood samples were taken over 4 hours then distal duodenal mucosa was biopsied endoscopically. Incorporation of tracers into protein was determined by isotope ratio mass spectrometry and preparative gas chromatography. Protein synthesis was calculated relative to intracellular free amino acid labelling. Protein and nucleic acids were measured by standard methods. **Results:** Protein/DNA ratios were reduced in patients with CD (9.2 ± 1.6 (SD) mg/ug v 13.0 ± 2.2 mg/ug, respectively; $p < 0.05$) suggesting that mucosal cell size was reduced in patients with CD. RNA/DNA ratios were identical in each group. Duodenal mucosal protein synthesis was markedly elevated in CD patients compared with the C subjects, whether determined by incorporation of the iv or ig infused tracers (iv CD v C 3.58 ± 0.45 (SD) v $2.26 \pm 0.22\%/h$; ($p < 0.01$) ig CD v C $2.34 \pm 0.52\%/h$; ($p < 0.01$). Labelling of mucosal intracellular amino acids was threefold higher when tracer was given ig than iv, but there were no differences between the groups, suggesting that the higher rate of protein synthesis measured with ig tracer in the CD patients is not the result of differential precursor labelling or luminal tracer malabsorption. **Conclusions:** The results suggest that despite the villous atrophy and the reduced mucosal cell size observed in CD patients, mucosal protein synthesis is elevated by between 50 and 200%, suggesting a concomitantly abnormal cell metabolism in addition to the high rate of protein breakdown or cell loss in coeliac disease.

W86

NUCLEAR EXPRESSION OF ANTI ENDOMISIAL ANTIBODIES

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We investigated the time course of EMA positivity disappearance in 14 patients in which diagnosis of coeliac disease was performed by jejunal biopsy. Patients were followed-up for 6-8 months. During this period serum samples were obtained monthly. All patients showed a complete histological remission at the second biopsy, performed after 6-8 months of gluten free diet.

The mean time of disappearance of EMA positivity, was 66 ± 41 days. Nevertheless in 12 patients a nuclear fluorescence was observable after EMA positivity disappearance. This nuclear fluorescence was not evident anymore, after further 78 ± 40 days.

In 2 patients, nuclear fluorescence was never observed during the follow-up period. To rule out the possibility that the nuclear fluorescence on monkey esophagus substrate might be the expression of Antinuclear antibodies (ANA) in patients sera, we analysed the prevalence of ANA positivity using HEp-2 substrate.

We performed the test in each patient at the three relevant time-points: EMA disappearance, nuclear fluorescence appearance and nuclear fluorescence disappearance.

The prevalence of ANA-HEp-2 positivity was of 21%, 18% and 0% respectively, suggesting that nuclear fluorescence on monkey esophagus substrate, represents expression of different antibodies. Data suggest that the presence of nuclear fluorescence only, has to be considered as expression of EMA positivity.

W88

A STUDY OF THE GROWTH OF BACTERIA AND FUNGI IN PARENTERAL NUTRITION SOLUTIONS IN THE PRESENCE OF TAUROLIN

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Catheter related infection (CRI) remains a serious complication of prolonged central parenteral nutrition (PN). Taurolin, a derivative of a naturally occurring aminosulphonic acid, has antimicrobial activity without significant toxicity; it is stable in PN solutions. The purpose of this study was to determine the *in-vitro* activity of Taurolin in two PN solutions against a range of organisms including isolates from patients with CRI. A lipid containing "all in one mix" (L) and a dextrose containing solution (D) were studied.

Dilutions of Taurolin were made in Mueller-Hinton Broth (MHB) and solutions L and D in the range 3g/l to 0.1g/l in a microtitre plate, and a standardized inoculum of organism added to each well. Colony counts were performed after overnight incubation at 37°C. Taurolin activity was expressed as the minimum bactericidal concentration (MBC) (i.e. the concentration at which 99.9% of the inoculum was killed). Fourteen strains of bacteria and one strain of yeast were tested, including 9 isolates from cases of CRI.

Taurolin MBCs varied from 0.4g/l to 1.6g/l in solution L, and 0.4g/l to 3g/l in solution D with no significant difference between the two solutions for any of the organisms tested.

We believe we are the first to investigate the antimicrobial activity of Taurolin in PN solutions. Our data suggest that the incorporation of Taurolin into parenteral nutrition fluids may be useful in the prevention or treatment of recurrent CRI.

W89

THE REDUCTION OF LOCAL COMPLICATIONS FROM PERIPHERAL INTRAVENOUS NUTRITION.
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The peripheral route is now the first choice for the administration of short-term intravenous nutrition, as it avoids the major complications associated with central venous cannulation. The main indication for peripheral catheter removal is the development of local complications, notably thrombophlebitis. The aim of this prospective study was to determine if the addition of heparin and hydrocortisone to the feed, and the application of a topical glyceryl trinitrate (GTN) patch over the catheter site delayed the onset of thrombophlebitis.

Forty-three patients were randomised to receive either a standard feed with no patch (control group, n=23), or a feed with added heparin and hydrocortisone, and a GTN patch applied topically (study group, n=20). The arm was examined daily, and the catheter removed if signs of PVT were evident.

Results: The two groups were well matched in terms of indications for feeding, and side and choice of vein. The catheters in the study group survived longer (12.4 versus 6.7 days (mean) $p<0.05$), caused a lower incidence of thrombophlebitis (6 versus 13 episodes of PVT $p<0.05$). The time of onset of thrombophlebitis was delayed in the study group (15.3 versus 6.4 days (mean) $p<0.05$).

Conclusion: The addition of heparin, hydrocortisone and a GTN patch significantly reduces the incidence of thrombophlebitis in patients receiving intravenous nutrition via a fine-bore peripheral catheter.

W91

DIRECT MEASUREMENT OF PORTAL VEIN FLOW IN PATIENTS WITH TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT SHUNTS - A NEW MODEL FOR THERAPEUTIC STUDIES?
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Study of pharmacological modulators of the portal circulation rely upon indirect measurements of portal pressure gradient, and portosystemic collateral blood flow [azygos vein flow]. Transjugular intrahepatic portosystemic stent shunts [TIPSS] allow direct vascular access to the portal vein.

METHODS: We have studied 12 patients with cirrhosis and a TIPSS in situ. A reverse thermodilution catheter was positioned through the shunt into the portal vein, and portal vein flow [PVF] was measured. Portal vein pressure [PVP] and right atrial pressure [RAP] were recorded, the portal pressure gradient [PPG] being PVP minus RAP.

RESULTS: The mean resting PVF was 768 +/- 80 ml/min [mean +/- SEM]. There was a significant difference between resting inspiratory and expiratory flows [1027 +/- 107 and 610 +/- 65 ml/min respectively: $p=0.035$]. At rest the PPG was 9.5 +/- 0.9 mmHg with no variation with respiratory excursion. On deep inspiration the PVF rose significantly above resting inspiratory values to 1494 +/- 159 ml/min [$p=0.014$]. RAP fell marginally on deep inspiration increasing PPG slightly. Valsalva manoeuvre caused a dramatic initial rise in PVF followed by a sustained fall as the manoeuvre was continued. Leg raising to 60 degrees from horizontal caused no significant change in PVF [763 +/- 123 cf 784 +/- 136 ml/min] or portal pressure, whilst RAP rose transiently. Manual abdominal pressure caused no change in PVF, however release of pressure caused a fall to 689 +/- 140 ml/min [$p=0.035$]. PVP rose with pressure but RAP remained constant.

CONCLUSIONS: PVF is constantly varying particularly with respect to respiratory excursion, however PVP remains relatively constant. Our method gives direct continuous results and presents itself as a unique means of studying drugs acting on the portal circulation in portal hypertensive patients with hepatic outflow resistance removed.

Chronic liver disease W90-W100

W90

INTENSIVE SCLEROTHERAPY DOES NOT PREVENT RECURRENCE OF OESOPHAGEAL VARICES.
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The records of 59 patients with bleeding varices who had undergone successful endoscopic sclerotherapy and who were followed - up for a minimum of 2 years after sclerosis of varices, were studied. 47 patients had cirrhotic, 8 non-cirrhotic and 4 extra hepatic portal hypertension. 16 patients (27%) had endoscopic recurrence of varices: one within 6 months, 8 (50%) within 2 years, and 14 (87%) within 3 years of sclerosis. In 2, varices recurred 5 and 8 years after sclerosis. (Mean : 28; Median 23; Range : 6 - 96 months).

27 patients (46%) developed post-sclerotherapy strictures and dysphagia. In 11 (41%) stricturing was mild, requiring a single dilatation. In 16 (59%) stricturing was more severe: a mean of 4.1 dilatations (median=2; range : 2 - 24) was required.

We calculated an index of intensity of sclerotherapy (I.I.S.) for all patients : (I.I.S. = total volume of sclerosant / time to sclerosis). In those who developed strictures the mean I.I.S. was 3.7 (Median 3.2) compared with 1.5 (Median 1.4) in those without strictures ($p=0.0001$); the mean time to sclerosis was significantly shorter: 20.1 weeks vs. 37.8 weeks ($p=0.0012$); the mean volume of sclerosant per session was significantly bigger : 11.2 mls vs 7.2ml ($p = 0.0003$) and the frequency with which sclerotherapy was administered was significantly greater : median inter-sclerotherapy interval was 3.4 weeks compared to 5.1 weeks in those without strictures ($p=0.0005$). Thus the stricture patients had received much more intensive sclerotherapy.

Variceal recurrence rate was not significantly different in these two groups. Of 27 patients with strictures 9 had recurrent varices (33%); of the 32 with no strictures, 7 had recurrent varices (22%), ($p = 0.33$).

Thus, intensive sclerotherapy which leads to more rapid sclerosis of varices at the cost of developing severe, fibrous stricturing of the oesophagus, does not protect the patient from variceal recurrence.

W92

THE EFFECTS OF ADENOSINE BLOCKADE UPON THE PORTAL CIRCULATION IN PATIENTS WITH CIRRHOSIS.
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Adenosine is a potent vasodilator important in the physiological control of liver blood flow and which mediates mesenteric hyperaemia after food and alcohol. Previous studies have suggested its role in the pathophysiology of portal hypertension. Theophylline blocks adenosine receptors and therefore may lower splanchnic and collateral flow and so reduce portal pressure gradient [PPG].

METHODS: Ten patients with cirrhosis were studied [9 alcohol-related, 1 PBC; mean Childs score: 7.4]. The free and wedged hepatic vein pressures, and azygos venous blood flow [AzBF] were measured before and after the administration of 240 mg oral theophylline elixir. Heart rate [HR] and mean arterial pressure [MAP] were also recorded.

RESULTS:

Time [min]	HR [bpm]	MAP [mmHg]	PPG [mmHg]	AzBF [ml/min]
0	74.7 +/- 4.7	101.1 +/- 6.2	18 +/- 1.2	537 +/- 106
30	75.8 +/- 5.1	98.7 +/- 4.1	-	454 +/- 97
60	77.4 +/- 4.6	96.5 +/- 4.8	16.9 +/- 1.2*	418 +/- 96+

* $p<0.05$, + $p=0.097$ compared to baseline on paired testing. PPG or AzBF fell in all patients. In 3 patients a fall in PPG was associated with either a rise or no change in AzBF. No adverse symptoms were experienced with theophylline administration.

CONCLUSION: Theophylline significantly reduced PPG and tended to lower AzBF as well without causing significant systemic circulatory disturbance. This implicates adenosine in the maintenance of the splanchnic hyperaemia of cirrhosis and its blockade may be beneficial clinically. Portal haemodynamic changes with theophylline occur by more than one mechanism.

PROTON MRS IN CHRONIC HEPATIC ENCEPHALOPATHY
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Proton magnetic resonance spectroscopy (³¹P MRS) may be utilised to investigate cerebral metabolism in patients with chronic hepatic encephalopathy (CHE).

The study population comprised 26 patients with biopsy-proven cirrhosis and 14 healthy volunteers. On the morning of MRS study, patients had psychometric, EEG and full clinical assessments. They were then classified as neuropsychiatrically unimpaired (n=5) or as having subclinical (n=10) or overt (n=11) CHE.

In vivo cerebral ¹H MR spectra (TR 1500 ms, TE 130 ms) were acquired at 1.5 Tesla using a 3-D CSI technique. Spectra were analysed from the occipital and temporal cortex and the basal ganglia. Peak area ratios of choline (Cho), glutamine and glutamate (Glx) and N-acetylaspartate (NAA), relative to creatine (Cr) were calculated. There were significant reductions in mean Cho/Cr and elevations in mean Glx/Cr in the patient population, which correlated with the severity of CHE (Table 1).

Table 1: Mean metabolite ratio from basal ganglia with normal reference ranges

neuropsychiatric status (n)	Cho/Cr (0.63-1.13)	Glx/Cr (0.06-0.12)
unimpaired (n=5)	0.78	0.13
subclinical HE (n=10)	0.67	0.39*
overt HE (n=11)	0.49*	0.85***

significant difference from reference population *p<0.05; ***p<0.005

The variation in cerebral ¹H MR spectra with neuropsychiatric status may be of use in diagnosis of subclinical encephalopathy and affords the possibility of monitoring disease activity in patients with CHE.

TIPSS occlusion and the role of biliary venous fistula
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Transjugular intrahepatic portosystemic shunt (TIPSS) is a relatively new method of reducing portal pressure and treating the complications of portal hypertension. Shunt insufficiency due to stenosis or occlusion is common and is the major cause of clinical complications such as variceal rebleeding and reaccumulation of ascites. The aim of this study was to assess the pathology and the possible pathogenetic mechanisms involved in shunt occlusion following TIPSS.

Patient and methods: Over 45 patient years of follow up (longest 2.8 years) 14 of the 56 (25%) patients with TIPSS have developed shunt stenosis. 8 patients had stenoses of greater than 70%. The contents of the shunt in these 14 patients were biopsied using endoscopy biopsy forceps followed by balloon angioplasty. Five livers were obtained at post mortem (3) or at liver transplantation (2). Cholangiography was performed on 3 of these explanted livers which were then perfused and fixed with formaldehyde. The shunts were dissected out of the liver with a rim of about 2 cm of the surrounding liver tissue, sectioned, stents opened and the contents of the shunt and the surrounding liver examined macroscopically and histopathologically after routine stains and with immunohistochemistry.

Results: At repeat portography 7 of the 8 patients (1 was transplanted) showed significant shunt stenosis. Three were managed by insertion of parallel shunts and the other 4 were treated with shunt dilatation. The former 3 have had no further problems whereas the latter patients have developed significant re stenoses. Organising thrombus was found in all 8 patients and bile was incorporated in the thrombus in 4. Biliary epithelium was found in 2. Biopsies from patients with mild stenosis were inadequate for analysis. Three of the 5 explanted livers showed evidence of shunt stenosis of which 2 were severe and 1 was mild. Pathological examination of the occluding material showed organising thrombus containing bile and a granulomatous inflammatory response. This was associated with a transected bile duct and the degree of stenosis was related to the size of the bile duct transected. The shunts free of bile showed no stenosis. Cicatrization of the intrahepatic bile ducts in the vicinity of the shunt was demonstrated at cholangiography.

Conclusion: Shunt occlusion following TIPSS is a consequence of formation of a biliary - venous fistula following introduction of the shunt. The degree of stenosis is closely related to the size of the bile duct transected. This is made possible by the incomplete nature of the wire mesh stent and has implications for shunt design and the management of patients with blocked shunts.

A prospective evaluation of haematological alterations following TIPSS
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Haematological changes in chronic liver disease may result from hepatocellular failure, portal hypertension and altered plasma volume. TIPSS is an effective modality of reducing portal hypertension and provides access to the portal system for direct pressure measurements. The aims of this prospective study were to (a) to assess the incidence and severity of haemolysis and its course following TIPSS and (b) assess changes in spleen size and any relationship to changes in the platelet and white cell count, and haemoglobin concentration.

Materials and methods: Twenty three patients undergoing TIPSS with a mean follow up of 8 months (se 1.2) were studied. Males : females was 13 : 10 and the mean age was 53.6 years (se 1.7). Full blood count, reticulocyte count, serum haptoglobin, urinary haemosiderin, examination of the peripheral blood smear and spleen size (ultrasonography) were measured prior to and 3, 7 and 30 days after TIPSS and 6 months thereafter.

Results: Seven patients (30.4%) developed haemolysis which was clinically significant in 3 (13%). This settled spontaneously with endothelialisation of the stent. Portal pressure gradient was reduced from a mean of 21.9 (se 1.6) to 9.5 (se 1) (p<0.001) mm Hg, 10.6 (se 1.5), 13.9 (se 1.1) and 13.3 (se 2) at 0, 3, 9, and 15 months respectively following TIPSS. Haemoglobin concentration improved significantly from a mean of 8.9 (se 1.6) to 11.3 (se 11.9) (p<0.05) at 3 months which was sustained 15 months after TIPSS. Significant change in spleen size and platelet count occurred with reduction in the former from 16.9 (se 1.1) to 13.7 cm (se 2.4) (p<0.01) and in the latter from 85.9 (se 8.4) to 135.3 X 10⁹/l (se 16.8) (p<0.01). The changes in both these parameters were most notable in the first 3 months following which the levels did not change significantly. No significant correlation were found between the changes in the portal pressure gradient, spleen size and platelet count. There was no significant change in the white cell count.

Conclusions: The results of this study indicate that (a) TIPSS is useful for reducing splenomegaly and improving thrombocytopenia, (b) there is no correlation between the change in the portal pressure gradient, spleen size and platelet count and (c) transient, significant haemolysis occurs in about 13% patients following TIPSS. TIPSS therefore, we believe, may be considered a treatment for hypersplenism in cirrhosis.

Analysis of prognostic variables in the prediction of variceal rebleeding, stent failure, encephalopathy and early mortality following TIPSS.
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The aim of this study was to analyse prognostic variables that may predict shunt insufficiency, variceal rebleeding, encephalopathy and early mortality following TIPSS.

Methods: Sixty four consecutive patients with TIPSS were studied. Mean age was 56.3 years (s.d. 10.4), 37 were males and 27 were females. TIPSS was performed for variceal bleeding (49), refractory ascites (6), portal gastropathy (6), embolisation of a spontaneous shunt (1) and 1 each for hypersplenism and painful splenomegaly. Of the patients with successful shunts thirteen were Child grade A, 22 were grade B and 20 were grade C. Cirrhosis in 41 was alcohol related, primary biliary cirrhosis in 6, cryptogenic cirrhosis in 7, viral hepatitis in 5, autoimmune chronic active hepatitis in 2, alpha1 antitrypsin deficiency in 1, noncirrhotic portal fibrosis in 1 and amyloidosis in 1. Patients have been followed up clinically, biochemically and radiologically (Doppler ultrasonography and portography) for 45 patient years (longest 2.8 years). The univariate association between individual prognostic factors and post treatment encephalopathy was tested by the Chi squared or Wilcoxon rank sum tests and multiple logistic regression used to test the significance of factors adjusted for one another. Cox's proportional hazard regression was used to test the univariate and multivariate significance of the other 3 outcomes.

Results: TIPSS was performed successfully in 56 patients (87.5%). Twenty two patients have died and 9 have been transplanted. Twelve patients died within 30 days of TIPSS and was predicted independently by the presence of active infection (p<0.05) and by severe liver disease (Child C, p<0.01). Shunt insufficiency was predicted by an initial portal pressure gradient of greater than 18 mmHg (p<0.01); variceal rebleeding by the need for mechanical ventilation (p<0.01) and lower Childs grade (Child A, p<0.05). Encephalopathy following TIPSS was only predicted independently by the presence of encephalopathy prior to the procedure (p<0.001).

Conclusions: The results of this study indicate that (a) early mortality occurs in 71% patients with Childs C cirrhosis and sepsis, (b) portal pressure gradient of greater than 18 mmHg predicts shunt insufficiency, (c) mechanical ventilation and low Child score predict variceal rebleeding and (d) encephalopathy is individually predicted by its presence prior to TIPSS. These groups require special consideration and prophylactic measures. These observations will however, need to be confirmed in a prospective study.

W97

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC STENT-SHUNT (TIPSS) INSERTION AS A PRELUDE TO ORTHOTOPIC LIVER TRANSPLANTATION (OLT) IN PATIENTS WITH SEVERE PORTAL HYPERTENSION

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It has been postulated that TIPSS insertion in selected patients awaiting OLT may alleviate portal hypertension, optimise their preoperative clinical course and facilitate surgery. Between November 1992 and May 1994, 8 patients with end-stage cirrhosis, portal hypertension and severe gastroesophageal varices underwent TIPSS insertion prior to OLT (median interval 30 months; range 1-82 weeks). There were no procedure related complications and recurrent variceal haemorrhage was controlled in all patients. Comparison was made with cirrhotic patients with severe portal hypertension and varices in whom OLT was undertaken during the same period but without prior placement of TIPSS (n=10). The two groups were matched with respect to age, sex and Child's grade. There were two post-operative deaths in TIPSS patients, neither of which were TIPSS related. No significant differences (NS) were observed in operative times or perioperative transfusion requirements between the two groups (unpaired T-test) (Table).

(Median values)	TIPSS	No TIPSS	
Recipient hepatectomy (mins)	180	208	NS
Time to portal venous bypass (mins)	166	197	NS
'Warm ischaemia' time (mins)	60	59	NS
Total operation time (mins)	457	487	NS
Red Cell Concentrate (units)	8	7	NS
Fresh Frozen Plasma (units)	9.5	11	NS

Perivascular fibrosis at the porta hepatis and hepatic venous confluence was encountered in TIPSS patients, but did not prevent safe and satisfactory surgical dissection. Stent malposition with protrusion into the superior mesenteric vein and suprahepatic vena cava occurred once and was associated with portal vein thrombus.

TIPSS placement in the preoperative management of patients with severe portal hypertension is a feasible option which does not preclude successful liver replacement, and 'buys time' for liver transplant candidates at risk of recurrent variceal haemorrhage. Accurate stent placement is important to avoid compromise of the recipient venous trunks.

W98

HEPATIC ³¹P MRS IN CHRONIC GRAFT REJECTION

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Hepatic phosphorus-31 magnetic resonance spectroscopy (³¹P MRS) is a non-invasive tool which provides information on hepatic metabolism *in vivo*. Sixteen patients were examined at various intervals following liver transplantation. Four individuals had biopsy-proven evidence of chronic ductopenic rejection and 12 had good graft function. Reference data were acquired from 23 healthy volunteers who had no history or clinical evidence of liver disease.

Hepatic ³¹P MR spectra were acquired with pulse angle 45° and repetition times of 5s and 0.5s. Peak area ratios of phosphomonoesters (PME), inorganic phosphate (Pi) and phosphodiester (PDE), relative to βATP were calculated from spectra acquired at TR 5s.

There were no spectral abnormalities in the 12 patients with good graft function. However, the four patients with chronic ductopenic rejection all showed a significant elevation in PDE/ATP and a PME/ATP which was marginally elevated or at the upper end of the reference range.

The elevation in PDE/ATP is probably multifactorial and may reflect an increased signal from bile in these cholestatic patients. The marginal increase in PME/ATP is probably due to increases in levels of phospholipid substrates, reflecting increased hepatocyte regeneration.

Table 1: Hepatic metabolite ratios in patients with chronic graft rejection with normal reference ranges.

Metabolite Ratio	Patient 1	Patient 2	Patient 3	Patient 4
PME/ATP (0.24 - 1.44)	1.23	1.03	0.95	1.44
Pi/ATP (0.44 - 1.48)	0.51	0.63	1.1	1.31
PDE/ATP (3.03 - 4.05)	4.17↑	5.08↑	4.56↑	5.20↑

W99

HEPATIC COPPER STATUS IN NEONATAL RATS AND EFFECTS OF RETRORSINE

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In mammals, high liver copper (Cu) and metallothionein (MT) levels decrease rapidly after birth with a concomitant rise in serum caeruloplasmin (Cp). This study investigates the neonatal changes in rat Cu status and the effect of the pyrrolizidine alkaloid retrorsine (RET) fed to the mother. RET acts synergistically with Cu to cause liver damage and Cu accumulation (Gut 1992; 33: S37).

2 groups of 4 female Wistar rats with new-born litters were fed for 3 weeks either control (CON) or RET (50mg/kg food) diet. At set intervals, at least 2 pups from each litter were weighed, sacrificed and the livers removed for analysis of Cu by atomic absorption spectrophotometry and MT by silver saturation. Serum samples were assayed for Cp using the o-dianisidine dihydrochloride method.

CON hepatic Cu levels rose after birth and declined from day 11. Serum Cp levels rose from day 8 and MT levels fell from the maximum at day 4. However, RET hepatic Cu levels rose progressively throughout the suckling period. Cp levels fell at day 8 and MT declined from birth. Mean RET liver and body weights were lower than equivalent CON.

Day	Liver Cu (µg/g dry wt)	Caeruloplasmin (IU)	Metallothionein (µg/g)			
	CON	RET	CON	RET	CON	RET
0	87,108	141 ±23	28 ±3	27 ±2	719,280	542 ±93
4	169 ±17	218 ±19	30 ±2	31 ±2	795 ±143	462 ±143
8	184 ±20	288 ±14	25 ±1	30 ±3	359 ±63	292 ±51
11	228 ±14	346 ±14	30 ±1	23 ±3	512 ±110	155 ±34
15	213 ±29	488 ±43	34 ±2	22 ±4	446 ±172	114 ±36
18	178,132	514,651	42,47	25,15	291,318	189,129
21	76 ±8		48 ±3		202 ±22	

Data shown as individual values where n<3 or, mean ± SEM where n≥3.

Thus, RET passing to neonatal rats via breast milk causes (1) active accumulation of hepatic Cu (2) a fall in serum Cp and (3) a decrease in hepatic MT levels. This effect is probably due to RET metabolites impairing protein synthesis. Accumulation of liver Cu but reduction of Cu binding proteins could result in free Cu and explain the synergistic hepatotoxicity of Cu and RET.

W100

SIGNIFICANT TRANSFUSIONAL IRON OVERLOAD DURING TREATMENT OF HAEMATOLOGICAL MALIGNANCIES.

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Improved survival after treatment for haematological malignancies has led to increased interest in causes of post-treatment morbidity. During treatment, these patients require supportive transfusions to maintain an adequate haemoglobin. Transfusional iron overload is a well recognised sequelae of multiple transfusions, though the long term clinical significance of the iron load in these patients is not known.

We studied 15 long term survivors (3-18 years, mean 8.1) of haematological malignancies treated with various chemotherapeutic regimens and supportive transfusions as required to maintain a haemoglobin of approximately 10 g/dl. All patients were initially screened with routine biochemical liver tests, ferritin and hepatitis B and C status. Those with abnormalities of ferritin and evidence of liver dysfunction were further screened to exclude other coincidental liver disease. Six patients with evidence of liver dysfunction and iron overload proceeded to a liver biopsy to quantify hepatic iron and obtain histological grading.

We found a high degree of variability in transfusion requirements (20-123 units, mean 52) during treatment. There was no relationship found between the chemotherapeutic regimen used and the amount transfused nor the liver dysfunction. Iron overload as measured by raised ferritin, was present in 11/15 and evidence of hepatic damage, as measured by raised transaminases, was present in 6/15. Ferritin levels correlated significantly with the amount of transfused iron (r²=0.603). Transaminase levels gave no indication of the degree of iron overload.

The liver biopsy iron content was significantly elevated (92-331 mg/g, mean 20.9) and correlated strongly with iron transfused (r²=0.779). Published data suggests that hepatic fibrosis is induced with liver iron concentrations in excess of 22mg/g (dry wt). Sufficient iron was present to place 2 patients at risk of liver fibrosis and in 2 others the hepatic iron was just below the fibrotic level. Histological grading varied between haemosiderosis grade 1-3 and correlated with both amount transfused and with liver iron content.

Our results suggest that transfusion requirements during treatment of haematological malignancies may be a source of substantial iron overload sufficient to lead to chronic liver damage. These patients should be screened for iron overload and venesection should be considered.

Surgery W101-W109

W101

THE ROLE OF LAPAROSCOPY IN AIDS

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Gastrointestinal pathology requiring surgical intervention is a common problem in the management of AIDS and HIV disease. Laparotomy is poorly tolerated in advanced AIDS with low CD4 counts.

This study has examined the presentation, AIDS status, CD4 count, operative treatment, final diagnosis and outcome in 14 cases which were treated laparoscopically. These represented 14 of the 24 (58.3%) major abdominal cases treated surgically over a two year period (1992-1993) at the Chelsea and Westminster hospital.

RESULTS

All the patients were male with a median age of 37.5 (29-54). They could be divided into two groups, one needing urgent surgical intervention and the second requiring elective surgery to obtain tissue from an intra-abdominal mass or lymph node.

In group one laparoscopic appendicectomy and cholecystectomy was performed as well as laparoscopy for a perforated viscus and for diagnosis of pain. Three cases also required laparotomy but the surgical access required was limited by localisation of the pathology.

Group two consisted of patients with established AIDS and a lower median CD4 count than group one (49 Vs 60). Laparoscopy was able to locate and obtain tissue for diagnosis in four cases. Four cases also required laparotomy to obtain tissue safely after the disease was localised.

The 30 day mortality was 28.6% (4/14), two from each group and the three month mortality was 54% (7/13). These cases represent patients with advanced AIDS who may not have been offered conventional laparotomy due to their poor condition.

CONCLUSION

Laparoscopy should be the first line operative measure in these patients to combine the advantages of reduced surgical trauma, lower morbidity and exposure of the surgical team to blood products. These cases are ideally managed within dedicated units because both the role of laparoscopy and the medical management of AIDS are constantly evolving.

W103

INSTRUMENT SAFETY DURING LAPAROSCOPIC CHOLECYSTECTOMY

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The incidence of serious complications from laparoscopic cholecystectomy lies between 1% and 6%. The nature of minimally invasive surgery is such that when distracted the surgeon may leave cannulated instruments unattended in the abdomen and resting on, or attached to delicate structures. This is potentially dangerous as unattended instruments may result in damage by puncture, traction or burn. This study was performed to determine the occurrence of this hazard during laparoscopic cholecystectomy.

External video recordings were made of 13 laparoscopic cholecystectomy operations and analyzed using a VHS video player with an actual time display in hours, minutes and seconds (h:m:s). The number of times and duration an instrument was placed into the abdomen but left unattended by the surgeon or assistants was recorded. The surgeons were unaware of the purpose of the study at the time of surgery.

A total of 17h35m18s of operation video tape was analyzed. Instruments were left unattended for 27% of the total operating time (4h44m33s) with a median duration of 9s (1s-17m28s). The median number of occasions instruments were unattended was 36 (range 14-62) (total for all operations - 468). The median non-attendance time was 15m54s (5m24s-1h20m39s). A non-attended instrument was inadvertently knocked, leant upon or allowed to fall whilst in the cannula on a median of 12 occasions (6-28) (total for all operations - 181). An attached electrosurgical instrument was left unattended for a median of 18s (0s-1m49s). This comprised 0.5% of the total operating time.

These data show that during standard laparoscopic cholecystectomy instruments were left unattended for a considerable period, often moved without control and when attached to an electrosurgical generator. To reduce risk during laparoscopic surgery instruments should be held in view of the laparoscope while within the abdominal cavity or withdrawn.

W102

TECHNIQUE OF LAPAROSCOPIC SPLENECTOMY USING A POWERED VASCULAR LINEAR STAPLER WF Anthony Miles, J Donald Greig, Graeme Wilson, Stephen J Nixon, Dept of Surgery, Western General Hospital, Edinburgh, EH4 2XU, Scotland.

Elective splenectomy by "classical" surgery is a major operation with an associated morbidity. The spleen, essentially an end-organ, is amenable to laparoscopic dissection. We describe the technique and results of laparoscopic splenectomy. Since 1992 twenty five patients have been considered for elective laparoscopic splenectomy. Indications for operation were: ITP (12 patients), HIV infection (7), acute haemolytic anaemia (3) and lymphoma (1). Under general anaesthesia with the patient in the right lateral position, two cannulas are inserted in the midline and two in the left upper quadrant. Following full mobilisation of the spleen an EndoGIA 60™ powered vascular linear stapler (Autosuture Co, UK) is fired across the thinned splenic hilum. The detached spleen is placed in a retrieval bag and removed by morcelation or via a Pfannenstiel incision if required for histology.

Two patients were unsuitable for laparoscopic dissection, one because the spleen was too large (>1kg), the other because of dense adhesions from previous surgery. Twenty one of the remaining 23 patients had successful laparoscopic dissection and vascular isolation of the spleen. Two immediate conversions occurred in the first half of the series because of uncontrolled bleeding. There was no 30 day mortality. The mean post operative stay was 6.5 days for the first half of the series and 4 days for the second half. The mean operating time in the last 12 patients was 100 minutes.

Laparoscopic splenectomy offers considerable benefit in terms of reduced surgical trauma, pain and in-hospital stay for debilitated patients.

W104

RISK OF POST-OPERATIVE DEATH IS HIGH AFTER FAILED ENDOSCOPIC THERAPY FOR BLEEDING ULCER C.P.Choudari & Palmer K.R.

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We examined the hypothesis that patients who continue to bleed or rebleed from peptic ulcer despite endoscopic treatment are at particular risk of post-operative death because of delays in a definitive surgical operation.

Post-operative mortality was recorded in 227 patients (group 1) who underwent urgent surgery for peptic ulcer haemorrhage between Jan 1985 and Dec 1988, when endoscopic therapy was unavailable. This was compared to the post-operative mortality of 50 patients who underwent a similar range of surgical operations for bleeding ulcer following failure of endoscopic treatment (group 2). This group was derived from a total of 342 patients in whom endoscopic injection or heater probe therapy was attempted for ulcer bleeding over the period June 1990 - April 1994. All patients receiving endoscopic therapy had either active arterial bleeding or a non bleeding visible vessel.

The overall mortality of the 342 patients in whom endoscopic therapy was attempted was 5%. Post-operative mortality in group 1 was 12%, compared to 22% in group 2 ($p < 0.05$). 7 group 2 patients rebled after surgery; 4 of these died. The mortality of patients treated endoscopically for bleeding ulcer is low. The high post-operative mortality of group 2 may be either due to endoscopy related delay in surgery or to the probability that this group had sustained more severe haemorrhage than that of group 1 patients. The challenge remains identification of the patient subgroup who are destined to fail endoscopic therapy and who should undergo urgent surgery.

W105

GASTRIC FUNDAL TONE AND PERCEPTION OF THE INTRATHORACIC STOMACH AFTER RADICAL OESOPHAGECTOMY
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Background: In normal subjects, gastric relaxation occurs both following distension and meal ingestion. **Aim:** We studied the relaxation responses of the intrathoracic stomach during progressive gastric distension in post oesophagectomy patients to determine the contribution of the intrinsic and extrinsic nervous system. **Patients and Method:** Five patients were studied (age: 41 to 75, sex: M-2, F-3), following subtotal oesophagectomy with transposition of the stomach. After an overnight fast a 1200ml polyethylene inflatable bag was sited in the gastric fundus and connected to a pressure recording device. Three Pressure/Volume (P/V) curves were recorded. First and second were performed in the fasted state, the third following ingestion of 250ml isotonic liquid meal. P/V curves were made by measuring pressure in response to bag inflation in 50ml increments of air. Perception at each volume was recorded using a graded score. **Results:** The mean pressure of the first curve was significantly higher than that of the second indicating distension induced relaxation, but there were no significant differences between the second and the fed curve indicating a loss of meal related relaxation (first: 14.66 (8.12-23.4), second: 10.95 (6.43-20.3), $P < 0.05$, fed: 7.48 (7.28-16.4)). Unlike normal subjects who felt increasing discomfort no patients have any discomfort or pain indicating complete extrinsic denervation. **Conclusions:** The transposed intrathoracic stomach demonstrated relaxation to mechanical stretch of the wall, but not to feeding. Afferent denervation during surgery probably accounts both for this loss of adaptive relaxation to food and the loss of perception of distension.

W106

FACTORS ASSOCIATED WITH FUNCTIONAL OUTCOME IN ILEOANAL POUCH CONSTRUCTION FOR ULCERATIVE COLITIS
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Functional outcome after pouch surgery is variable. One hundred and fifty five pouches for ulcerative colitis were reviewed, 22 had been excised, 8 still have a defunctioning ileostomy and 3 were unsuitable for follow up. One hundred and twenty two questionnaires were dispatched and 80 were returned. The questionnaire provided data on functional score, the patient's social function, patient satisfaction, underlying anxiety score (Spielberger STAI), their Health Locus of Control (HLC, Wallston), coping style (MBBS, Miller) and psychiatric screening (GHQ, Goldberg).

Type of anastomosis (sutured versus stapled), Crohn's disease and pouchitis were associated with a poor outcome, whereas pouch type (W or J pouch), operative difficulties (pelvic fibrosis) and post operative complications (sepsis, ileoanal stenosis, small bowel obstruction, fistulae) were not.

Pouch function assessed by a 12 point score was satisfactory (0 - 3) in 43%, tolerable (4 - 6) in 28% and poor (> 6) in 29%. There was a significant positive correlation between functional outcome and (1) age, (2) social activity score, (3) satisfaction score and (4) anxiety score but not coping styles and Health Locus of Control.

Multiple regression analysis to predict functional outcome only gave significant levels for Spielberger's anxiety scale and patient's age ($t=4.77$, $t=2.21$).

For future prospective studies with the aim of predicting outcome measurement of the patient's underlying anxiety seems to be worth exploring.

W107

HOW LONG DOES A POUCH LIVE - CAUSES OF POUCH FAILURE AND LIFE EXPECTANCY OF THE ILEOANAL POUCH
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180 ileoanal pouches constructed over a 10 year period (154 for Ulcerative Colitis and 26 for Familial Adenomatous Polyposis) were reviewed regards excision rate and defunctioning rate. 22 pouches were excised to date, 8 remain defunctioned.

The reasons for excision were: ischemia in 6 cases, pelvic sepsis in 5, severe stenosis in 2, chronic pouchitis in 4, underlying Crohn's disease in 2, poor function in 2 and fistula formation in 1. The reasons for defunctioning were: Crohn's disease in 1, pelvic sepsis in 5, ileoanal stenosis in 2. Of all the pouches, pelvic sepsis occurred in 24 cases, ileoanal stenosis in 35 and chronic pouchitis in 14.

The projected overall survival rate (Life table analysis) at 5 years was 81.8% (confidence interval 75 - 88%). Beyond 7 years, it became unreliable (insufficient data).

Split into subgroups, the table shows the corresponding survival rates:

Subgroup	Total number	No. excised (defect)	Survival at 5 years	Confidence interval
FAP	23	1	94.4%	84% - 100%
Polyposis coli	3	0	100%	
UC	141	16 (8)	83%	76% - 90%
Crohn's	10	3	70%	42% - 98%
Redo	3	0 (2)		

There was a very strong association between pouch failure and pelvic sepsis (Pearson's $p < 0.0001$), but only a weak one with pouchitis ($p = 0.074$) and ileoanal stenosis ($p = 0.047$).

Conclusion: Ischemia, pouchitis and sepsis remain problems in pouch surgery. Pouch failure can occur even years after initial operation. Longterm follow up is highly recommended.

W108

AUDIT OF FUNCTION, SATISFACTION AND IRRITABLE BOWEL SYNDROME FOLLOWING RESTORATIVE PROCTOCOLECTOMY FOR ULCERATIVE COLITIS AND FAMILIAL ADENOMATOUS POLYPOSIS
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The results of restorative proctocolectomy for ulcerative (UC) and familial adenomatous polyposis (FAP) are thought to be satisfactory, for FAP they are even described as 'spectacular'. Postal questionnaires were sent to 144 pouch patients. Ninety eight responded (UC $n = 80$), FAP $n = 18$). Type of procedure, length of hospital stay and complications were already recorded.

There was a higher complication rate (ileoanal dehiscence, ileoanal stenosis, fistulae, small bowel obstruction) in the UC: 58 in 38 patients (47%) compared with FAP, 9 in 6 patients (33%). Pouchitis occurred in 21 UC patients (26%) and in 2 FAP patients (11%).

Functional outcome using a 12 point scoring system was slightly worse in UC than in FAP (not significant). Patient satisfaction (derived from 4 questions) and social activity (9 questions) were closely related to functional outcome. Satisfaction with the outcome was significantly less in FAP ($P < 0.001$), whereas the social activity score was similar.

Irritable bowel syndrome (IBS) before the diagnosis of UC or FAP occurred in 47.5% and 22.2% respectively. There was no relation to function in UC but patients with IBS had a poorer functional result in FAP.

The poor patient satisfaction in FAP stresses the need for extensive counselling pre-operatively since they are all asymptomatic and have no experience with a stoma.

W109

A 5 YEAR AUDIT OF SPHINCTER REPAIR (1988 - 93)
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We decided to audit the results of sphincter repair because of a result of a change of surgical policy: All patients had a complete sphincter defect and all patients had been followed up for more than 6 months.

Sphincter repair was performed in 6 men: 3 posterior defects associated with fistula operations and 3 anterior defects from perineal trauma associated with urethral injury and pelvic fractures. Only one of the 3 posterior repairs was associated with any residual minor incontinence, which was cured by graciloplasty. All of the anterior defects had required a stoma at the time of injury; despite this and complete reconstruction of the anterior rectum, only one patient is continent.

Eighteen women had sphincter repairs, one was a lateral repair from previous fistula surgery with a good result. The remaining 17 defects were anterior reconstructions and included anterior levatorplasty, Z-plasty as well as sphincter repair. Only 2 had a covering stoma (both delayed for 48 hours). Seven patients had persistent incontinence (major 3, minor 4) and two have had successful repeat repairs. Factors in this female group associated with persistent incontinence were age over 50 years (3 of 4), obesity (2 of 3), post-operative sepsis (3 of 4) and gross perineal descent (5 of 8).

These results raise the role of a stoma, particularly in obese and elderly women having sphincter repair.

T111

INHERITED COAGULOPATHIES PROTECT AGAINST INFLAMMATORY BOWEL DISEASE
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Introduction: Only 3 patients with ulcerative colitis and 1 patient with Crohn's disease are reported occurring in association with haemophilia. Histological studies have revealed mesenteric vessel microthrombi in both Crohn's and ulcerative colitis, and there is haematological evidence of a persistent activation of coagulation in those with inflammatory bowel disease (IBD). Heparin has been reported as being beneficial in ulcerative colitis. This study tested the hypothesis that concurrent IBD and an inherited disorder of coagulation is a rare event. **Methods:** 9,562 patients with haemophilia A or B, or von Willebrand's disease, are managed by 129 UK Haemophilia Directors. All Directors were contacted by questionnaire or telephone to determine if they were either caring for or had cared for a patient with IBD and haemophilia or von Willebrand's. Those responding positively were sent a second questionnaire to obtain further details. The number expected to develop IBD in this population was determined using data from all 5 UK studies with age-specific data. Significance between observed and expected numbers was tested using Chi-squared with Yates correction.

Results: 13 patients with IBD were identified. 4 had Crohn's disease compared with an expected 15.60-19.28 ($p<0.005$). 9 had ulcerative colitis compared with an expected 19.43-28.84 ($p<0.025$). 3/4 with Crohn's and 1/9 with colitis had required surgery. The significant difference between observed and expected cases was explained neither by gender or age distribution of the study population, nor by the possible confounding effect of HIV infection. IBD in this group did not appear to carry a particularly poor prognosis; no patient had died due to a combination of these diseases. **Conclusion:** Both Crohn's disease and ulcerative colitis occur significantly less frequently than would be expected in those with inherited disorders of coagulation. This observation supports the hypothesis that thrombotic vascular events are important in the development of IBD.

Inflammatory bowel disease T110–T119

T110

APPENDICECTOMY, TONSILLECTOMY AND INFLAMMATORY BOWEL DISEASE
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Aims. Recent studies have indicated an inverse relationship between appendicectomy and ulcerative colitis (UC). The explanation for this is not clear but it has been suggested that removal of the appendix with its associated lymphoid tissue may protect against subsequent development of UC. However we hypothesized that factors which promote appendicitis may be protective rather than appendicectomy *per se*. Therefore the aim of the present study was to determine the frequency of primary appendicectomy in Oxfordshire patients with inflammatory bowel disease (IBD). The frequency of tonsillectomy was also examined.

Methods. A prospective questionnaire-based survey of 197 consecutive patients with UC (mean age 50.4) and 117 patients with Crohn's Disease (mean age 41.3) was carried out. Primary appendicectomy was defined as operation for 'suspected appendicitis'. Two hundred and forty three unselected dermatology outpatients (mean age 43.3) at a neighbouring hospital acted as a control population.

Results. Primary appendicectomy was significantly less common amongst UC patients than controls (age/sex adjusted odds ratio 0.20, confidence limits 0.07-0.53, $p<0.0005$, Mantel-Haenszel test) but not reduced in patients with Crohn's disease (CD). Of the 7 UC patients who had had a primary appendicectomy, the operation was carried out in 5 before the onset of their disease. The frequency of tonsillectomy in both groups of IBD patients was no different from the controls. However tonsillectomy was significantly more common in CD patients who had undergone colectomy (7/10) compared to those who had had other resections or no surgery at all (23/107, $p<0.005$, Fisher's exact test, two-tailed).

Conclusions. These results are consistent with the hypothesis that factors which promote appendicitis may protect against UC. Alternatively the failure to develop appendicitis may confer later susceptibility to UC. For patients with CD, prior tonsillectomy may be a risk factor for subsequent colectomy.

T112

AN OPEN TRIAL OF ANTI-PLATELET THERAPY IN ACTIVE CROHN'S DISEASE USING PICOTAMIDE, A THROMBOXANE ANTAGONIST. **CE Collins, *A Forbes, DS Rampton.** GI Science Research Unit, The Royal London Hospital and *Department of Gastroenterology, St Mark's Hospital, London.

Thromboxane A₂ may be an important inflammatory mediator in Crohn's disease (CD). Activated platelets may play a pathogenic role in multifocal microvascular infarction in CD. Picotamide (Sandoz, Italy), a thromboxane receptor antagonist / synthesis inhibitor, is widely used in Italy as an antiplatelet agent, in prophylaxis of ischaemic heart and peripheral vascular disease. The aim of this study was to assess the therapeutic effect of picotamide in active CD.

METHODS: 9 outpatients with active CD (CDAI 150-300) who had not received steroids or changes in other medication during the previous 4 weeks, were treated with oral picotamide (600 mg bd) for 6 weeks. Progress was assessed by clinical and laboratory indices.

RESULTS: (given as medians (IQR); P values derived from paired t tests for week 0 vs week 6 scores or values).

score / value	week 0	week 2	week 4	week 6	P
n	9	9	9	8	
CDAI	231(203-293)	189(112-229)	172(72-181)	136(61-187)	0.001
stools / week	31(26-36)	26(13-30)	18(9-22)	16(6-29)	0.01
abdominal pain	11(6-12)	5(2-9)	2(0-5)	1(0-5)	0.006
well-being	9(7-14)	6(3-10)	2(1-6)	2(0-5)	0.002
platelet count	299(239-415)	346(266-397)	323(248-399)	334(231-401)	NS
CRP mg/l	23(5-38)	15(5-23)	24(5-39)	21(5-34)	NS
albumin g/dl	42(38-42)	41(38-43)	41(35-43)	41(39-43)	NS

1 patient was withdrawn at week 4 with no improvement in symptoms and a fall in serum albumin. 5/9 patients entered remission (CDAI<150) during treatment and 1 further patient had done so by follow-up 6 weeks after treatment. 5 of these 6 patients remain well after 7 months (4-9) follow-up. 2/8 patients who completed treatment later required surgical intervention (abscess drainage, right hemicolectomy for ileal stricturing). No adverse events occurred.

CONCLUSION: Picotamide safely ameliorates symptoms in ambulant patients with active CD; this effect is maintained after cessation of therapy. A controlled study is warranted.