ALTERED GENE EXPRESSION OF C-ERBB3 DURING OESOPHAGEAL TUMORIGENESIS: APPLICATIONS FOR SURVEILLANCE.

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Conventional analysis of the biological nature of oesophageal mucosa requires multiple biopsies which may not be representative of oesophageal lesions such as Barrett’s metaplasia. The use of cytology potentially overcomes these problems but is labor intensive and many subtle morphological features are lost in the processing. In this regard application of the molecular cell sciences can overcome these problems and in addition offer genetic alternatives.

Abnormalities of differentiation characterise earlier stages of Barrett’s tumorigenesis and we studied c-erbB3 a tyrosine kinase receptor known to be expressed differentially in oesophageal lesions. We studied protein expression by immunohistochemistry and Western blot analysis an RNA expression by RT-PCR and Northern blot analysis in a range of tissue.

c-erbB3 expression is strongest in Barrett’s gastric-type metaplasia particularly in the differentiated compartment. In specimens with dysplasia and those with intestinal metaplasia c-erbB3 immunoreactivity is reduced. Furthermore the majority of adenocarcinomas had diminished or absent immunoreactivity especially in the poorly differentiated lesions. Western blot analysis confirmed the protein corresponded with the mature c-erbB3 protein of 160 kDa.

Northern blot analysis demonstrated that the 6.4 kb c-erbB3 mRNA transcript was weakly expressed even in non-dysplastic mucosa. Using paired primers to both 5' and 3' ends, RT-PCR confirmed that c-erbB3 mRNA in Barrett’s mucosa is relatively strongly expressed and that expression in dysplastic specimens and invasive neoplasia decreases steadily and is lost in poorly differentiated lesions.

RT-PCR indicates that oesophageal cytology from dysplastic mucosa expresses less c-erbB3 compared with non-dysplastic metastasis. Brushings were taken in 1cm sweeps from metaplastic epithelium during endoscopy and c-erbB3 was reduced or absent in cytology corresponding with areas of intestinal metaplasia and dysplasia, respectively.

In conclusion we have elucidated that alterations in c-erbB3 expression occur, either at the translational or transcriptional level, early in oesophageal tumorigenesis. Furthermore we have applied this biomarker of tissue differentiation to cytological preparations from upper alimentary epithelia in one of the first studies of its kind.


Primary Gastric Lymphomas (PGL) are B cell lymphomas of mucosa associated lymphoid tissue (MALT) and, as with gastric carcinoma are associated with Helicobacter pylori (H. pylori). In early low grade MALT tumours, anti-Helicobacter therapy may lead to a regression of the lymphoma. It has been recommended that all patients (pts) with low grade disease should be treated medically rather that with surgery. In our experience, PGL presenting as mucosal disease is uncommon and anti-Helicobacter therapy may therefore be inappropriate for our cases.

The notes of all pts with PGL from 1973 - 1992 were reviewed. Specimens were assessed independently by 2 Histopathologists with additional immunocytochemistry and examined for H. pylori using conventional and Giemsa staining. Analysis was by Kaplan Meier survival curves.

Symptoms were the same as for gastric cancer, 49 pts with a mean age of 65 years (range 25 - 84yrs) were identified. The male : female ratio was 1.5 : 1. H. pylori was present in 80 %. Only 1/18 pts with low grade PGL had marked bulky disease. One pt died from anti - Helicobacter therapy with no evidence of recurrence 2 years later.

All others were treated by surgery (23) and/or chemo-radiotherapy (20).

Overall 5 year survival, irrespective of histological grade of tumour was 40%. Survival in pts with low grade disease was 60 %, intermediate grade, 20 % and high grade 36 % (NS). There was a non significant trend for an improved prognosis in those pts treated by surgery. H. pylori may be a co-factor in the pathogenesis of PGL. Most pts, even those with low grade MALT tumours present with advanced tumour bulk and on current evidence would be unsuitable for anti - H. pylori treatment.

These pts should be treated by agreed medical and / or surgical means.

UROKINASE-TYPE PLASMINOGEN ACTIVATOR (uPA) AS A PROGNOSTIC INDICATOR IN COLORECTAL CANCER.

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Introduction: Destruction of basement membrane is important during tumour spread and the progression from non-metastatic to metastatic colorectal cancer. Urokinase-type plasminogen activator (uPA) is implicated in the breakdown of the extracellular matrix to be involved in cancer progression. The prognostic significance of uPA has not been determined in large bowel cancer.

Aim: To correlate uPA immunohistochemical staining with clinical and pathological features, and survival in patients with non-metastatic colorectal cancer extending beyond the bowel wall (Dukes’ B). Patients: 70 patients with Dukes’ B colorectal cancer presenting for potentially curative surgery.

Methods: Formalin-fixed paraffin embedded sections were stained for immunohistochemistry using a monoclonal antibody against the B-chain of uPA (American Diagnostic Inc., CT). Epithelial and stromal positivity were scored independently by a pathologist blinded to clinical details and patient outcome. Epithelial staining was graded as: -) <2%; 1) 2-20%; 2) 21-50%; 3) 51-80%; 4) >80%. Stromal staining was graded: -) few cells; 2) focal cellular aggregates; 3) multifocal aggregates; 4) diffuse.

Results: Grade 1 epithelial uPA reactivity was found in 9 cases, grade 2 in 5 (7%), grade 3 in 8 (12%) and grade 4 in 57 (81%). Grade 1 uPA stromal staining was seen in 16 patients (23%), grade 2 in 22 (31%), grade 3 in 19 (27%) and grade 4 in 13 (19%). A positive correlation between both forms of staining was seen (p=0.036). No significant association was found between epithelial or stromal reactivity and patient age, sex, tumour site, tumour size, histological type, tumour grade, vascular invasion or perineural invasion. High levels of epithelial uPA (grade 4) correlated with tumour necrosis (p=0.03). Five year survival estimated by the Kaplan-Meier method was 61% for patients with grade 1, 2 and 3 epithelial uPA positivity (n=13) versus 58% for those with grade 4 (n=57) (Logrank analysis, p=0.01). Stromal reactivity was not significantly related to survival. Regression analysis identified epithelial uPA reactivity as an independent prognostic factor within the Dukes’ B group (relative risk 4.25; p=0.04).

Conclusion: These results suggest that epithelial uPA reactivity may be a useful marker of tumor aggressiveness in Dukes’ B colorectal cancer.

ASPIRIN AND NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) USE AND SYMPTOMATIC COLORECTAL CANCER: A CASE-CONTROL STUDY. R.F.A. Logan, J. Little, S. Smith & P. Hirst. University Dept. of Public Health & Epidemiology, University Hospital, Nottingham, NG7 2UH, UK.

Several NSAIDs have been shown to inhibit the growth of experimental colonic cancers and there is increasing epidemiological evidence that regular NSAID use is associated with a reduced risk of colorectal cancer. We have examined analgesic use in a case-control study of symptomatic but not advanced colorectal cancers. Data on analgesic and other drug use has been obtained by interview from 240 patients with Dukes A or B stage colorectal cancer. 208 community controls and 214 controls recently in hospital for elective surgery. Subjects were interviewed at home between June 1989 and March 1992. Unconditional logistic regression was used to estimate relative risks (RR) and 95% confidence intervals (1) adjusted for age, sex and social class.

The RR of a colorectal cancer in those reporting any aspirin use (145 subjects) was 0.82 (0.51-1.3) in comparison with community controls and 1.47 (0.9-2.4) with hospital controls. In those reporting other NSAID use (76 subjects) the RR was 0.65 (0.3-1.2) with community controls and 0.61 (0.3-1.1) with hospital controls. The inverse associations were greatest for prescribed aspirin and NSAID use (65 subjects) with RR’s of 0.57 (0.3-1.1) and 0.52 (0.3-1.0) in comparison with community and hospital controls respectively.

For comparisons with community controls inverse associations with NSAID use were consistent and were strongest for self-prescribed aspirin taken at least weekly (16 cases and 24 controls. RR v. no use 0.50 (0.3-1.0). There were no consistent associations with paracetamol use with the RR’s for any paracetamol use being 1.05 (0.7-1.5) and 0.53 (0.4-0.7) in comparison with community and hospital controls respectively.

These findings agree with our results for colorectal adenomas and cancers detected by screening and further support the hypothesis that NSAID use protects against the development of colorectal cancer.
INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN PRODUCTION IN NORMAL AND NEOPLASTIC COLONIC EPITHELIUM

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Insulin-like growth factors (IGFs) are expressed by many different cell types and have profound effects on cell growth and function. The biological activity of the IGs is in part regulated by the presence of binding proteins (IGFBPs) which modulate the IGF-receptor interaction.

Using human colonic carcinoma-derived cell lines (HT29, Colo and SW) addition of IGF-I to cells cultured in serum-free conditions resulted in an increase in DNA synthesis (\(^{3}H\)-thymidine incorporation into DNA) of ten-fold for HT 29 cells and seven-fold for the other two cell lines. Minimal stimulation occurred at an IGF-I concentration of 30 nM and was cell density dependent (maximal responses at 5x10^5 per cm). Des-(1-3)IGF-1, which does not bind to IGFBPs but stimulates the IGF-1 receptor, increased DNA synthesis to a much lesser extent (1.2-2 fold increase) in these cells, implicating a role for IGF-IGFBPs in facilitating growth. All three cell lines produced IGFBPs when their serum-free conditioned media were analysed by Western ligand blots. A 30kD IGFBP was common to all cells (probably IGFBP2), HT29 and SW cell lines also produced a 25kD IGFBP (probably IGFBP4) and the SW cells alone produced a 29kD IGFBP. Short term primary cultures from normal human colonic epithelium and adenomas, adenomas and carcinomas was established and their IGFBP production in serum-free conditions assessed. Initial results show that the carcinoma cells secreted IGFBPs into the medium, in contrast to cells derived from the normal colonic epithelium which failed to secrete any detectable IGFBP. These were two IGFBPs of 35kD and 30kD, the principal protein being the 30kD species also seen in all three established cell lines (IGFBP2).

The other IGFBP had molecular weights of 38kD (probably IGFBP3).

These findings suggest that the presence of IGFBPs may enhance the mitogenic properties of IGFs on colonic epithelium in vivo and may play a role in the pathogenesis of colonic carcinoma.

VITAMIN D AND RETINOID X RECEPTOR mRNAs ARE EXPRESSED IN HUMAN COLORECTAL MUCOSA AND NEOPLASMS.

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Epidemiological studies reveal a protective role for 1,25(OH)\(_{2}\) vitamin D (D\(_{3}\)) against colorectal cancer, and D\(_{3}\) has previously been shown to have an antiproliferative effect at supraphysiological doses in vitro. D\(_{3}\) has been proposed for use as a therapeutic agent in colorectal carcinoma. However, Scatchard analysis demonstrates high affinity, low capacity binding sites in only 32% of tumours implying that D\(_{3}\) would only have limited chemotherapeutic value. D\(_{3}\) action is mediated by the vitamin D receptor (VDR) in all D\(_{3}\) responsive tissues. A second D\(_{3}\) signalling pathway, activated by VDR/ retinoid X receptor (RXR) heterodimers, has recently been identified. The aim of this study was to determine whether receptors involved in D\(_{3}\) signalling are expressed in human colonic mucosa and neoplasms. The functional integrity of both D\(_{3}\) signalling pathways was assessed by growth studies of HT-29 cells treated with D\(_{3}\), synthetic D\(_{3}\) analogs and 9-cis retinoic acid (the ligand for RXR).

VDR and RXR expression was determined in 22 carcinomas, 2 adenomatous polyps and paired normal mucosa, in addition to HT-29 cells, by Northern analysis. (\(^{3}H\)Thymidine uptake and cell counts were determined in HT-29 cells following treatment with each agent. Full length VDR, RXR\(_{a}\) and RXR\(_{y}\) mRNAs were expressed in all tissues. RXR\(_{y}\) mRNA was not expressed. HT-29 cells expressed identical mRNAs and exhibited an antiproliferative response to physiological levels of D\(_{3}\) and analogues. Co-treatment with 9-cis retinoic acid resulted in a dose dependent blockade of D\(_{3}\) action.

In vivo and in vitro expression of VDR and RXR in all colonic mucosa samples and all tumours provides the full functional repertoire of receptors required for D\(_{3}\) signalling. The physiological effects of D\(_{3}\) and 9-cis retinoic acid on cell proliferation implies that both D\(_{3}\) signalling pathways are intact in HT-29 cells. These findings have important implications for the actions of D\(_{3}\) in the pathogenesis of colorectal carcinoma and the potential role of D\(_{3}\) analogues in their therapy.

ALTERED E-CADHERIN EXPRESSION IN COLORECTAL TUMORIGENESIS: IN VIVO AND IN VITRO COMPARISONS.

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The serial molecular events during colorectal tumorigenesis have been intensively studied. In particular recent evidence suggests that cell-cell contact may be disrupted at various stages in dysplastic polyps. E-cadherin has been identified as an important cell adhesion molecule which is expressed on all epithelial cells and as an important biomarker of differentiation in alimentary neoplasia. Little is known, however, with regard to the alterations in expression of this molecule in cellular and glandular locations in premalignant colonic lesions.

We assessed, therefore, 15 specimens of normal colonic mucosa, 45 colonic adenomas, 20 metastatic polyps, 55 colonic adenocarcinomas. Furthermore we investigated the expression of E-cadherin in a colonic cell line HCA-7 which has multiple colonies with different degrees of differentiation. We utilised the antibody HECD-1 to assess the morphological changes by immunohistochemistry and also to assess the quantitative changes by Western blot analysis.

E-cadherin is expressed predominantly on the cell membranes in normal tissue. In metastatic polyps E-cadherin immunoreactivity was comparable with normal tissue. During increasing grades of dysplasia E-cadherin expression changes from a membranous to a cytoplasmatic distribution. Well-differentiated adenocarcinomas expressed greater E-cadherin than poorly-differentiated lesions. Western blot analysis confirmed upregulation of the protein product in serial lesions from normal, microadenomatous and increasingly dysplastic lesions. The vast majority of the immunoreactivity corresponded to a band of 120 kDa.

In the HCA-7 colon cell line after 3 days growth to sub-confluence the fastest growing and invasive colonies expressed less E-cadherin than the well-differentiated colonies. After a 2 weeks of growth to confluence all colonies had increased membranous E-cadherin expression.

In conclusion E-cadherin expression is altered both in cellular distribution and quantitatively as colonic tumorigenesis progresses. It can be shown that membranous expression correlates with increased cellular differentiation in vivo and in vitro. It seems that errors in the intracellular distribution of E-cadherin in cell lines underlie the altered biological abnormalities in the early stage of tumorigenesis whereas in invasive colorectal lesions both factors may be altered and that this defect may be reversible.

IN VIVO AND IN VITRO GENE EXPRESSION IN COLORECTAL TUMORIGENESIS: A PUTATIVE MOLECULAR CELL MODEL.

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Selective identification of novel genes responsible for pivotal molecular events in tumorigenesis requires that a satisfactory experimental human model is available which can mimic the varied biological characteristics displayed in the adenoma-carcinoma sequence. In this regard the colonic adenocarcinoma cell line HCA-7 has multiple subcolonies which have different degrees of differentiation, proliferation and growth in xenografts. We studied four colonies which had progressive abnormalities; colony 3 very poorly differentiated, highly invasive, colony 1 (poorly differentiated), colony 6 (moderate differentiation, slow growth), colony 30 (well differentiated and forms glands in xenografts). In addition we studied clinical specimens of normal colonic mucosa (15), microadenoma (10), polyps with mild, moderate and severe dysplasia (45), colonic adenocarcinomas with varied degrees of differentiation (40).

Protein expression was studied in vivo and in vitro by immunocytochemistry, ELIZA and Western blot analysis.

The expression of the growth factors transforming growth factors \(\alpha\) and \(\beta\), the mucus muc-1, villin and the cell adhesion molecule E-cadherin were reproducible biomarkers of tissue differentiation in both in vivo and in vitro specimens. The growth factor cripo and ki-67 proliferative indices correlated well with aggressive biological activity in vitro and in vivo. Colonies 3 and 1 corresponded with invasive malignancies whereas colonies 6 and 30 corresponded with dysplasia and normal colonic mucosa, respectively.

In subsequent experiments we have been able shown that the sub colonies of the cell line can be manipulated, for example TGF-\(\beta\), E-cadherin and villin are upregulated and expression of cripo and proliferation indices reduced as differentiation is induced.

In conclusion we have developed a molecular in vitro model which allows aspects of human gene expression in colorectal tumorigenesis to be studied and manipulated. We are now testing novel genetic sequences utilizing this model.
W9

**ISOLATION OF HELICOBACTER PYLORI IN FAECES FROM PATIENTS IN THE UK - CONFIRMATION OF CULTURE**

**IDENTITY BY PCR. S.M. Leeds,** dyspepsia **PCR were samples A)**

The exact route of transmission of Helicobacter pylori remains unclear. Epidemiological studies suggest that faecal-oral passage is important. We have successfully cultured H. pylori from faeces and proceeded to confirm culture identity by PCR. **36 adults with subjects with dyspepsia in Cambridge were studied. H. pylori status was assessed by gasocopy with biopsy and/or a 13C urea breath test.** Fresh faecal samples were obtained from all subjects and processed immediately. Bacterial pellets, separated from stool samples, were plated onto selective growth media. **H. pylori grew** as tiny circular translucent colonies towards the periphery of the plates. Colonies were subcultured to obtain pure cultures of H. pylori which then underwent genotypic analysis by PCR.

The urease A gene of H. pylori is highly conserved and a specific DNA probe. We also attempted to identify the cytotoxin associated gene (cag A) which codes for a 130 kD protein that is highly specific for H. pylori. PCR was performed using primers from these two genes.

25 subjects had positive gastric biopsies or breath test for H. pylori infection, whilst 11 were negative. Faecal cultures of H. pylori were successfully obtained from 12 of the 25 positive subjects (48%). No growth occurred from the negative persons. Bacterial samples from 8 of the 12 successful cultures were then used for DNA amplification. The urease A gene was detected in 3 and cag A detected in 2. Our failure to confirm a genotypic identity for the remaining cultures was most probably due to a low cell yield of bacteria from the plates and, possibly, confounding technical reasons. Phenotypically, all the positive cultures were identical.

**Conclusion**

This study is the first to conclusively demonstrate that H. pylori can be cultured in faeces from adults in the UK. Fecal oral spread is therefore feasible and the isolation of H. pylori from faeces may become a useful diagnostic tool in future clinical practice.

W10

**REINFECTION OR RECURRENCE OF HELICOBACTER PYLORI INFECTION**

HX Xiai 4, DG Marshall2, HJ Windle3, CJ Smyth2, CT Keane1, CA O’Morain3

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Recurrence of H. pylori infection after apparent eradication occurs and results in duodenal ulcer relapse. The aim of this study was to determine whether reinfection or recurrence accounted for the recurrence. Over five years, 320 patients who were treated with colloidal bismuth subtrioxide 120 mg q.d for 4 weeks, metronidazole 400 mg and tetracycline 500 mg i.d for the first week had H. pylori eradicated, e.g. H. pylori was not detected by rapid urease test, histology and microbiology four weeks after end of the treatment. The infection, however, recurred in five of these patients during a period of follow-up (7 to 22 months), Pre- and post- treatment isolates from these patients were subcultured on chocolate agar and incubated under microaerophilic conditions for 3-5 days. Pure DNA were extracted with a phenol/chloroform/alcohol method and used for restriction endonuclease analysis (REA) with Hind III and PCR-based randomly amplified polymorphic DNA fingerprinting (RAPD) with a combination of 2-10 mer primers. Supernatants of bacterial cells after boiling in water bath were used for SDS-PAGE and the RAPD. SDS-PAGE,REA and RAPD showed that the pretreatment and recurrent isolates were identical for all the five patients. RAPD gave the most discriminatory fingerprints. DNA prepared by boiling the bacterial cells could be also used for RAPD and yielded reproducible fingerprints. In conclusion, recurrence or reinfection after apparent eradication is due to recrudescence, rather than reinfection, suggesting that vaccine against H. pylori might be useful to prevent H. pylori infection. RAPD is a reliable strain-specific typing method and can be easily done using unpurified DNA templates.

W11

**PERSISTENT EXCRETION OF HELICOBACTER PYLORI IN FAECES AFTER GASTRIC ERADICATION. S.M. Leeds,** dyspepsia **PCR were samples A)**

We have previously demonstrated that Helicobacter pylori can be isolated in faeces of dyspeptic patients colonized with this organism. Of 25 subjects with gastric colonisation, H. pylori was present in stool samples of 12. These subjects then underwent a 2 week course of DeNoi and metronidazole to eradicate the organism. One month after completion of this treatment, subjects underwent a standard 13C urea breath test to confirm eradication. At this stage, a further stool sample for H. pylori culture was obtained. Samples were homogenised in 0.1M sodium phosphate buffer prepared under microaerophilic conditions at 37°C. Samples were then plated at 15,000 g. The pellet produced was washed and an aliquot plated out on H. pylori selective growth media (Dent supplemented Columbia agar base with 10% w/v horse blood added). Plates were incubated microaerophically and colonies of H. pylori subcultured.

All 12 subjects had a successful eradication, as determined by the breath tests. However, in 3 of these persons H. pylori was still isolated from faeces. These results demonstrate persistent faecal excretion of the organism after gastric eradication. This is indicated that H. pylori can be harboured elsewhere in the gastrointestinal tract and that persistent faecal excretion could potentially represent an important route of autoinfection.

W12

**Early serological assessment of Helicobacter pylori eradication.**

P. Patel, M.A. Mandy, A. Bond*, S. Khulasi, N. Molineaux, J. Levy & T.C. Northfield, Depts of Medicine and Immunology, St. George’s Hospital Medical School, London, UK.

**Background** Serology has been shown to be of use in the assessment of eradication of H. pylori after treatment. However, the main disadvantage is that it is necessary to wait at least 6 months before obtaining reliable results. This is due to the slow fall in the total IgG response after successful treatment. Aim: To assess the fall in IgG response to different H. pylori antigens in order to identify antigens which could provide a more rapid assessment of eradication.

**Subjects & Methods** 21 patients with peptic ulceration who had undergone endoscopy were recruited. All were positive for H. pylori on either histology or rapid urease test. Serum was collected before triple therapy and at 2 and 6 months thereafter. Eradication status was assessed on histology and urease test at 2 months. Whole H. pylori were fractionated by SDS-PAGE and transferred onto nitrocellulose paper and probed with patients sera. The IgG response to different antigens was assessed using IgG conjugate and the ECL detection system (Amersham). The bands on the immunoblots were quantified using densitometry and the Collage programme. Results: There were 16 eradicators and 5 non-eradicators. The immunoblots showed that the percent fall in mean IgG reactivity between non-eradicators and eradicators to high molecular weight [HMW(>60K)] antigens was greater than that to a 60K or low molecular weight [LMW(<60K)] antigens.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>All bands</th>
<th>HAMW bands</th>
<th>60K band</th>
<th>LMW bands</th>
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<tbody>
<tr>
<td></td>
<td>percent fall at 2 months</td>
<td>p value</td>
<td>percent fall at 6 months</td>
<td>p value</td>
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<tr>
<td>All bands</td>
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<td>0.06</td>
<td>29</td>
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<td>HAMW bands</td>
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<tr>
<td>60K band</td>
<td>28</td>
<td>0.28</td>
<td>44</td>
<td>0.0005</td>
</tr>
<tr>
<td>LMW bands</td>
<td>12</td>
<td>0.46</td>
<td>73</td>
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</table>

Using the optimal cut off point, the positive predictive value/negative predictive value for identifying eradicators at 2 and 6 months were 0.83/0.67 and 0.88/0.75 respectively using all antigens and 1.00/0.83 and 1.01/0.83 respectively using only HMW antigens.

**Conclusion** In eradicators the IgG response to HMW antigens falls more rapidly than that to other antigens. These results suggest that HMW antigens could provide the basis for a better test for assessing success of eradication treatment after 2 months.
**W13**

**Association of H. pylori with diminished adult height**

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**Background:** Other studies have noted that H. pylori infected adults (1) and children (2) are shorter than the uninfected. This finding has not received comment, nor have the effects of childhood living conditions which are so important in the aetiology of adult height and delayed puberty. There is also evidence that H. pylori infection is associated with diminished adult height.[40] In our study, we attempted to elucidate the mechanism by which H. pylori infection might cause diminished stature.

**Subjects and methods:** 401 intake

**Aim:** To confirm the association between diminished adult height and H. pylori seropositivity after controlling for childhood social class. 

**Results:** 380 children (95% caucasian) seen in a health screening clinic, of whom 24% were called up at random, 22% opportunistically asked to attend by their primary care physician, 44% were self referrals, and 11% who were older than the others were attending for influenza innoculations. The mean age was 47yrs, median 46yrs. Range 18-81, 47% male. A questionnaire was administered by a research nurse and serum was drawn for the determination of antibodies to H. pylori using an in-house ELISA which was 98% sensitive and 95% specific for the presence of infection. Height was measured using a stadiometer. Results were analysed using multiple regression with father’s occupation being coded as manual or non-manual and social class as six categories.

<table>
<thead>
<tr>
<th>male neg</th>
<th>male pos</th>
<th>female neg</th>
<th>female pos</th>
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</thead>
<tbody>
<tr>
<td>mean height,cm (n)</td>
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<td>mean height,cm (n)</td>
<td>mean height,cm (n)</td>
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<tr>
<td>&lt;30</td>
<td>171.7 (11)</td>
<td>173.7, 10 (0)</td>
<td>166.3, 1.4 (20)</td>
</tr>
<tr>
<td>30-39</td>
<td>172.9 (12)</td>
<td>171.1, 10 (0)</td>
<td>162.4, 1.1 (22)</td>
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<tr>
<td>40-49</td>
<td>176.4 (9.5)</td>
<td>176.1, 13 (20)</td>
<td>162.2, 0.8 (15)</td>
</tr>
<tr>
<td>50-59</td>
<td>175.1 (12)</td>
<td>175.4, 19 (10)</td>
<td>163.3, 1.0 (13)</td>
</tr>
<tr>
<td>60-69</td>
<td>173.5 (10)</td>
<td>173.5, 10 (0)</td>
<td>164.8, 0.3 (10)</td>
</tr>
<tr>
<td>70+</td>
<td>175.3 (7)</td>
<td>173.9, 14 (13)</td>
<td>158.8, 1.5 (10)</td>
</tr>
</tbody>
</table>

The difference in height between H. pylori -ve and -ve subjects adjusted for age, sex, current social class, and fathers occupation was 1.42cm, p=0.01. The adjusted mean for men alone was 1.9cm and for women 1.1cm.

**Conclusion:** H. pylori is associated with diminished adult height independently of childhood social class. The possibility that there is a causal association is good potential public health importance.

**References:**


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**W14**

**CELL PROLIFERATION IN HILOBACILLY PLYRIO ASSOCIATED GASTRITIS AND THE LONG TERM EFFECT OF ERADICATION THERAPY.**


**Introduction:** H. pylori (HP) is the cause of chronic (Type B) gastritis. Gastric cancer arises on a background of chronic gastritis and prospective epidemiological studies have suggested that it may be a major risk factor. Increased cell proliferation (CP) increases the likelihood of a neoplastic clone of epithelial cells emerging in the context of epithelial cell injury associated with HP gastritis (HPG).

We have measured antral CP in HPG and post anti-HP triple therapy. **Method:** Endoscopic biopsies of the antrum (2) were taken for in-vitro bromodeoxyuridine (BrdU) immunostaining. The Labelling Index (LI) was determined in the three zones of the gastric glands (Zone I = surface + gastric pit; Zone 2 = isthmus; Zone 3= gland base). At least 500 cells/zone counted in subjects with normal endoscopy + histology (n=12), HP-ve gastritis (n=10), HP+ve gastritis (n=42); [Duodenal ulcer=23; Non-ulcer=29], patients 4 weeks after completing successful (HPF I; n=20) or failed (HPF I; n=14) therapy and patients 6-18 months (mean=12) after successful (HPF I; n=8) or failed (HPF I; n=4) therapy. Results: Positive staining for BrdU varied in the same direction for all three zones. The majority were situated in Zone 2. Mean (SD) LI% of Zone 2 are as follows: Controls=15.1(2.2); HP+ve=10.3(1.8); HP-ve=17.9(1.1) [Ulcer=18.3(1.1), Non-ulcer=17.6(1.2)]; HPF I=12.0(1.9), HPF II=11.5(0.8), HPF III=11.7(3.3). CP was increased in HPG vs Controls and HP gastritis (P=0.0001; Tukeys Studentized Range). There was no difference in ulcer and non-ulcer subjects with HP (P=0.62; Student T-test). Antral CP fell 4 weeks after therapy whether or not HP had been eradicated (P=0.0000). Long term follow-up of those in whom therapy had failed had increased CP vs HPF ve subjects and HP+ve or HPF ve subjects 4 weeks after therapy (P=0.026).

**Conclusion:** HP infection causes increased gastric cell proliferation. In this way it may play a role in gastric carcinogenesis.

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**W15**

**INTERLEUKIN–8 AND TUMOUR NECROSIS FACTOR–α RNA IN ANTRAL MUCOSA OF DUODENAL ULCER PATIENTS: EFFECT OF ERADICATING H. PYLORI.**

SF Moss, J Davies, S Lecon, J Geaim. Royal Postgraduate Medical School, UK.

**The molecular mechanisms whereby H. pylori causes gastritis are unclear.** We investigated whether H. pylori affects mucosal synthesis of cytokines by examining the effect of eradicating the infection on mucosal gene expression of interleukin–8 (IL–8) and tumour necrosis factor–α (TNF–α).

The cytokines encoding IL–8 and TNF–α were measured in extracts of 5 antral biopsies by Northern blotting as described previously using appropriate 32P labelled cDNA probes. Extracts obtained before and after eradication of H. pylori from 9 infected patients with duodenal ulcers were run in adjacent lanes. Autoradiographs were quantified by laser densitometry and filters were re-probed for 18S rRNA to correct for uneven loading. Gastritis was assessed in 2 further biopsies by Raouw's method (Gastroenterology 1988;94:33).

Gastritis improved greatly after eradication of H. pylori; the median score fell from 5.7 (range 3.7–7.7) to 1.0 (1.0–1.7), P < 0.01. Neutrophils generally disappeared but some chronic inflammatory cells remained. Cytokine expression also fell significantly. The median TNF–α RNA/RNA ratio fell from 1.3 (0.7–2.7) to 0.6 (0.4–2.7), P = 0.02. The median IL–8 RNA/RNA ratio fell to a greater extent from 21 (5–50) to 1 (0–3), P = 0.004.

**Conclusion:** H. pylori antritis increases expression of IL–8 and TNF–α, implicating these cytokines in the pathogenesis of the gastritis. Chronic inflammatory cells remaining after eradication of H. pylori may have caused the less marked fall in TNF–α RNA.

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**H PYLORI AND IMPAIRED INHIBITOR CONTROL OF GASTRIC ACID SECRETION IN DU PATIENTS.**


We have previously shown that H. pylori positive DU patients have a 6-fold increased acid response to gastrin releasing peptide (GRP) and this is due to the combination of exaggerated antral gastrin response and exaggerated acid response to gastrin. Both defects fully resolve within one year of eradication of H. pylori. In addition to the exaggerated gastrin release, GRP also activates inhibitory control pathways of acid secretion. In the present study we investigated whether the increased acid response to gastrin during GRP stimulation is due to failure of an inhibitory control pathway of acid secretion.

The inhibitory control of acid secretion during GRP stimulation was examined in 9 H pylori positive DU patients and 9 H pylori negative healthy volunteers. It was assessed by comparing maximal acid output to exogenously administered gastrin-17 (G17) with maximal acid output to endogenous gastrin stimulated with increasing doses of GRP. The GRP was infused at 10, 40, 100, and 200pmol/kg each for 45 min.

**MAXIMAL ACID OUTPUT TO GRP STIM. TO EXOGENOUS a/b x 100**

<table>
<thead>
<tr>
<th>HP-ve</th>
<th>GASTRIN (a)</th>
<th>G17 (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.9</td>
<td>(3.9–6.6)</td>
<td>(18.0–5.6)</td>
</tr>
<tr>
<td>40.5</td>
<td>(22.4–8.1)</td>
<td>(40.1–8.5)</td>
</tr>
</tbody>
</table>

* Greater than HP-ve at p<0.01.

In true normals controls the maximal acid response to gastrin stimulated by GRP represented only 27% of that achieved by exogenous gastrin. This indicated that HP infected patients had an abnormal mechanism which was inhibiting the acid response to gastrin stimulation. In the HP-ve DU patients the maximal acid response to gastrin stimulated by GRP was significantly greater than that achievable by exogenous gastrin indicating that the inhibitory mechanism was much less effective.

In conclusion, these findings indicate that the exaggerated acid response to GRP in DU patients which is reversed by eradication of H pylori is due to impairment of an inhibitory control mechanism involved in the regulation of gastric acid secretion.
IS DEFECTIVE ACID CLEARANCE IMPORTANT IN SEVERE GASTRO-OESOPHAGEAL REFLUX DISEASE?
C P Barham, A Mills, D Alderson, University Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW.

Patients with oesophageal strictures and those with Barrett’s oesophagus represent severe gastro-oesophageal reflux disease. Impaired clearance of refluxed acid is thought to be an important contributor to oesophageal damage. Most methods for assessing acid clearance are indirect measurements made on fasted, immobile subjects studied over a short time. Acid reflux and clearance were studied under ambulant conditions using a portable pH/mannometry system. Study groups were: healthy control subjects (n=15), patients with acid induced strictures (n=14) and Barrett’s oesophagus (n=15). Measures of acid clearance included the number of peristaltic waves needed to return the pH to greater than four, the time taken to initiate a clearance contraction, the peristaltic wave interval and the longest single peristaltic wave interval per acid reflux episode.

Results

Controls Strictures Barrett’s

<table>
<thead>
<tr>
<th>Time to first clearance</th>
<th>Contraction (seconds)</th>
<th>Peristaltic wave interval</th>
<th>Peristaltic wave</th>
<th>Longest peristaltic wave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>38±5</td>
<td>199±3</td>
<td>62±7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(20-59)</td>
<td>(78-267)</td>
<td>(39-98)</td>
<td></td>
</tr>
</tbody>
</table>

Peristaltic wave interval (seconds) 68±6 230±3 109±9
(44-82) (125-283) (78-117)

Longest peristaltic wave interval (seconds) 55±7 339±2 142±2
(97-333)

Under ambulant conditions patients with oesophageal strictures have a gross abnormality of oesophageal acid clearance. Failure to clear refluxed acid is less significant in Barrett’s oesophagus.

** Median values and interquartile ranges, vs p < 0.001, * p < 0.05, vs vs p < 0.01, Mann Whitney U Test

EARLY EXPERIENCE OF THE USE OF ENDOSCOPIC ULTRASOUND IN AN UPPER G.I. SURGICAL UNIT.
A Watson, C Cope, Royal North Shore Hospital, Sydney, Australia.

Endoscopic ultrasound (EUS) has been reported as an accurate staging modality in upper G.I. cancer, particularly useful in oesophageal cancer, where loss of fat planes compromise the accuracy of CT scanning. The capital cost and expertise required preclude availability of the technique in all but a few centres. We report our preliminary experience of EUS in an upper G-I Surgical Unit. 27 patients underwent CT scanning and EUS using an Olympus EUIM system, 22 examinations were to stage oesophageal cancer and 5 to examine other lesions. Circumferential scans were performed along the whole oesophageal length at 7.5mHz to assess the degree of wall penetration and nodal enlargement. In 11 patients with oesophageal cancer who proceeded to surgery, EUS and CT findings were compared with operative and histological findings. Of the 11 patients with oesophageal cancer who proceeded to surgery, EUS accurately predicted the degree of wall penetration in 9 (82%) and nodal enlargement in 11 (100%). Corresponding figures for CT scanning were 73% and 35% respectively. Both EUS and surgery failed to distinguish between enlarged reactive and metastatic nodes in three patients (27%) overall, although concordance occurred with nodes greater than 1.5cms. 11 patients did not proceed to surgery, 10 because of locally advanced or metastatic disease and 1 with end-stage respiratory disease in whom EUS showed the tumour to be confined to sub-mucosa, which was successfully treated with laser photoacoagulation. 5 other patients had suspected sub-mucosal malignancy which was excluded in all cases by EUS, all patients remaining well at follow up.

Endoscopic ultrasound is more accurate than CT scanning in staging of oesophageal cancer, particularly in relation to nodal involvement. It enables inappropriate surgical intervention to be avoided in some patients and can identify some situations where local treatment may be considered with curative intent.

DYSPHAGIA AND DELAY IN TREATMENT FOR OESOPHAGEAL CARCINOMA.
IM Reid, TN Walsh, TPJ Hennessy, Department of Surgery, St. James’s Hospital, Dublin 8.

The incidence of oesophageal carcinoma is increasing in Western Europe. The prognosis is poor as diagnosis is often late. Greater awareness of the significance of dysphagia might result in earlier diagnosis and treatment.

The initial presentation and management of 43 patients with oesophageal carcinoma was assessed using a standard questionnaire, on presentation to the surgical unit. The median age was 67 years (range 40-83). Dysphagia was a significant early symptom in 35 patients (81%). On first consultation with their GP, 22 of these 35 patients (63%) were appropriately referred for further investigation, but 13 (37%) were prescribed medication with no further action initiated. 8 of 10 patients prescribed H2-blockers or Omeprazole found their symptoms improved. The median delay between onset of dysphagia and definitive treatment was 3.5 months (range 1-8 months). 7 patients (20%) waited six months or longer for treatment from the onset of dysphagia.

Delays in treatment were equally divided between delayed presentation by the patient, delay in onward referral by the GP and delays caused by hospital services. Hospital services were responsible for the longest delays.

Greater awareness of the significance of dysphagia could facilitate earlier diagnosis of oesophageal carcinoma. Anti-ulcer medication may mask symptoms of malignancy. Delay in obtaining out-patient appointments was a significant factor in late diagnosis.

HELICOBACTER INFECTION IS ASSOCIATED WITH OESOPHAGITIS IN PATIENTS WITH BARRETT’S OESOPHAGUS, T A Justin, R J C Steele, Dept of Surgery, University Hospital, Queen’s Medical Centre, Nottingham, NG7 2UH, UK.

Previous studies have been unable to demonstrate a relationship between Helicobacter pylori (HP) infection and oesophagitis, but the role of HP in patients with established gastro-oesophageal reflux is not clear. We have studied 30 consecutive patients undergoing endoscopy for surveillance of Barrett’s oesophagus. Biopsies of the gastric antrum and head and of the columnar-lined oesophagus were taken for urease testing to detect HP, and read at 24 hours.

Thirteen patients were HP positive in the antrum and four in the oesophagus, but no patient was positive in the oesophagus alone. Ten patients had oesophagitis above the Barrett’s segment, and there was a significant association between HP infection and oesophagitis (table).

Nine patients taking omeprazole, all HP(-) without oesophagitis, were excluded from the analysis.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>HP (+)</th>
<th>HP (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts.</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>69.3</td>
<td>71.5</td>
</tr>
<tr>
<td>Range (yrs)</td>
<td>49-82</td>
<td>43-79</td>
</tr>
<tr>
<td>Male:Female</td>
<td>9:3</td>
<td>6:3</td>
</tr>
<tr>
<td>No. with oesophagitis</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

No. with oesophagitis = 0.05 (Fisher’s Exact)

Barrett’s oesophagus is a reliable marker for gastro-oesophageal reflux, and in this group of patients we have found an association between oesophagitis and HP infection of the stomach. It is possible that HP may modify the refluxate such that oesophagitis becomes more likely.

Barrett's esophagus (BE) is considered a premalignant lesion, having a higher incidence in men than in women. Histopathology alone cannot predict the behaviour of BE. Therefore additional parameters are useful in the assessment of malignant progression. In previous investigations we have evaluated the role of immunostaining and the occurrence of numerical chromosome changes, defined by DNA in situ hybridization (ISH) or paraffin sections of BE from patients with and without adenocarcinoma (K. Krishnadath et al., Cytometry press 1994).

In this study we have investigated aneuploidy and chromosome aberrations by applying flow cytometric DNA probes, specific for chromosomes 1, Y and X, to 4-μm paraffin sections of 50 (33 male, 17 female) biopsy specimens from patients with BE. ISH data were compared with histopathological grading, p53 overexpression and DNA-FCM. Significant correlations were found between grade of dysplasia, DNA aneuploidy and positive p53 immunohistochemistry (p-values < 0.001, Trend-test). Grading also correlated significantly with loss of the Y chromosome in male biopsy specimens (Table 1).

In conclusion, we found aneuploidy, loss of the Y-chromosome and p53 overexpression to be markers for malignant progression in Barrett's esophagus. Further, non-isotopic in situ hybridization can be applied successfully to archival tissues, allowing investigation of genetic events in histologically preserved tissue sections.

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>n</th>
<th>Aneuploid</th>
<th>-Y</th>
<th>p53+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>9</td>
<td>2 (22%)</td>
<td>1 (11%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Low</td>
<td>12</td>
<td>4 (33%)</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>5 (56%)</td>
<td>7 (84%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>3 (100%)</td>
<td>3 (100%)</td>
<td>2 (67%)</td>
</tr>
</tbody>
</table>

Table 1: Results of ISH with specific DNA-probes and p53 immunostaining in biopsy specimens of 33 male patients.

Macroscopic Shape and Node Involvement in the Superficial Type of Oesophageal Cancer. Hironazu Nagawa, Shoichi Kaizaki, Yatsuyuki Seto, Osamu Tominaga, Tetsuchiro Muto. First Department of Surgery, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan.

There has been considerable controversy with regard to surgical strategies for superficial types of oesophageal cancer characterized by tumour invasion confined to the epithelium (EP), muscularis mucosa (MM), or submucosa (SM). The purpose of the present study was to determine the clinical results of patients who underwent oesophagectomy with regional node dissection (3 EP, 4 MM, and 26 SM cases). Tumour invasions of MM and SM were divided into 3 categories respectively (MM1, 2 and 3, SM1, 2 and 3) according to depth of invasion. Tumours were divided into 2 types according to macroscopic characteristics: 1) Tumours with and 2) without elevated components, and evaluated the relationships among macroscopic shape, depth of invasion, and node involvement.

RESULTS: All the tumours with an elevated component (n=19) invaded MM2 or more, and had node involvement excluding one case of MM2 invasion. On the other hand, tumours without an elevated component (n=14) showed depth of invading lesions (EP to SM3), and had no node involvement excluding one case of MM3 invasion.

<table>
<thead>
<tr>
<th>DEPTH</th>
<th>ELEVATED EP</th>
<th>MM1</th>
<th>MM2</th>
<th>MM3</th>
<th>SM1</th>
<th>SM2</th>
<th>SM3</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>0(0) 0(0) 0(0) 0(1) 3(1) 7(2) 7(6) 19(10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-)</td>
<td>3(0) 2(0) 2(0) 2(1) 10(0) 4(0) 2(0) 14(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses show numbers of patients with lymph node involvement.

Conclusions: The existence of elevated components is an important macroscopic feature suggesting submucosal invasion and node involvement in the superficial type of oesophageal cancer. Intensive treatment should be adopted for such tumours, while minimal localized resection may be feasible for tumours without elevated component.

A Predictive Assay for Response of Oesophageal Carcinoma to Chemoradiotherapy. N. Sheridan, T. Reid, C. Mothersill, C.B. Seymour, T. Naish, T.P. Hennessy. Dublin Institute of Technology, Kevin St., and Dept. of Surgery, St. James's Hospital, Dublin.

Combined chemoradiotherapy (chemoDXT) for patients with inoperable oesophageal cancer compared to chemoradiotherapy (cisplatin and 5-fluorouracil (5FU) added in solution to culture medium) or combined chemodXT. Tumours were cultured for a further 2 weeks, then fixed, stained and assessed. Growth inhibition was assessed for each tumour by comparing total growth area in treated and control flasks. Tumour explants grew successfully from 12 of 14 patients. Tumours from 5 patients showed a reduction of mean growth area greater than 60% after radiotherapy relative to the control culture from the same patient. All 12 tumours showed greater than 60% reduction of mean growth area after both radiotherapy alone and combined chemoradiotherapy.

These results clearly demonstrate that tumours from individual patients vary in response to therapy, particularly radiotherapy. This in vitro method of predicting tumour response from endoscopic biopsies may be helpful in treatment planning.


Members of the epidermal growth factor family have been identified as molecules which enhance events of pivotal importance in oesophageal tumorigenesis. Cripto is a 185-kDa protein which has a 37-amino acid region that shares considerable homology with other members of the EGF family. In colorectal tissue cripto is upregulated as tumourigenesis progresses and it is postulated that cripto can function as a dominantly acting oncogene, since overexpression of the cripto gene can lead to the transformation of epithelial cells and fibroblasts in vitro. We studied protein and messenger ribonucleic acid from normal oesophageal mucosa, gastric-type metaplasia, intestinal-type metaplasia, dysplastic mucosa and a range of tumours with altered differentiation by immunohistochemistry (performed by Prof. Bill Gullick, ICRF). In addition we studied the quantitative differences between neoplastic, dysplastic and non-metaplastic tissue by Western blot analysis.

Cripto is absent in normal oesophageal epithelium and detectable only in occasional cells of metastatic esophageal tissue. As the lesions become progressively more dysplastic cripto immunoreactivity increases in epithelial cells usually the neck and superficial glandular cells. Once invasive malignancy develops cripto is readily detectable compared even with surrounding 'normal' tissue. Well-differentiated tumours with an intestinal phenotype have a particularly increased cripto expression. In normal tissue surrounding adenocarcinomas cripto levels are also induced.

Western blot analysis confirmed that the majority of the immunoreactivity was against the mature cripto protein at 37 kDa, however, a band of approximately 29 kDa possibly corresponding to the secreted peptide is present in most specimens, particularly in intestinal-type neoplasia.

The specific expression of cripto in metastatic epithelium and the subsequent serial increase in expression of cripto-1 during oesophageal tumorigenesis suggests an important morphoregulatory role.
High-dose rate (HDR) intraluminal irradiation for esophageal cancer in clinical practice.

B.G. Taal1, G. Baris2, H. Booij3, C.C.E. Schakke-Koning1, Departments of Gastroenterology, Radiotherapy2, Netherlands Cancer Institute/ Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

In esophageal cancer intraluminal irradiation has been applied prior to or even without external radiotherapy for rapid tumor reduction and relief of dysphagia. Since the new High Dose Rate source (HDR) has become available the irradiation time could be reduced from several hours to 10 minutes resulting in a much more tolerable procedure from the patient's point of view. To evaluate the palliative effect of HDR intraluminal irradiation we performed a prospective study in two groups of patients with esophageal obstruction. Group A: 37 pt with only locally advanced disease, no metastasis: 26M, 11F, median age 76 yrs; adenocarcinoma 20 pt; squamous cell carcinoma 17 pt. Treatment: 10 GY HDR with 192-Iridium, 2 weeks rest followed by external beam irradiation of 40 GY/4 weeks. Group B: 26 elderly pt in poor general condition and/or with distant metastasis: 15M, 9F, median age 75 yrs; adenocarcinoma 15 pt; squamous cell carcinoma: 11 pt. Treatment: one session of 10 (n=20) or 12.4 GY (n=6) HDR.

Results: Group A: tumor response as demonstrated by barium meal and/or endoscopy; 9 partial and 8 near-complete and 10 complete remissions (overall 75%). Improvement of dysphagia: 19 (51%). Side-effects: minor acute esophagitis in 5 patients. Group B: tumor response: complete 1, total minor responses (42%). Subjective improvement: 35%. Side-effects: none. Duration of response: 3-4 months, almost equal to life expectancy.

Conclusions: 1. HDR is a safe and well tolerated procedure in patients with esophageal cancer. 2. Adequate palliation can be achieved by HDR alone in patients with a poor diagnosis. 3. HDR in combination with external beam irradiation results in effective tumor reduction and relief of dysphagia in patients with a more favorable prognosis due to only locally advanced disease.

OMEPRAZOLE VERSUS RANITIDINE IN THE TREATMENT OF SYMPTOMATIC MILD REFUX OESOPHAGITIS: A DUTCH MULTI-CENTRE TRIAL. B.P. Hazenberg1, A.A.M. Gerards2, G.H. de Groot (introduced by H.P.M. Festen)
The Dutch Reflux Study Group1 Refaja Hospital Dordrecht, The Netherlands

Several studies have proved omeprazole to be more efficacious than ranitidine on both healing and symptomrelief in patients with moderate and severe reflux oesophagitis (RO). However, in patients with only mild RO (Savary Miller, grade I and II), omeprazole and ranitidine are seldom compared. Therefore 243 patients (132 M, 111 F) aged 51.7 (15,4) (mean (SD)) year with symptomatic mild RO were randomised, to treatment with omeprazole 20 mg o.m. or ranitidine 300 mg (norte). An endoscopic examination was performed after 4 weeks treatment. For those patients not endoscopically healed after 4 weeks or who still had residual symptoms, there was a further 4 weeks treatment followed by a final endoscopy. After 4 and 8 weeks respectively 64.8% and 75.4% of the patients treated with omeprazole were both endoscopically healed and symptomfree. These figures were 24.0% and 33.1% for ranitidine (p<0.01).

After 4 and 8 weeks a significantly greater decrease in the presence of heartburn and refluxregurgitation was seen in the omeprazole group compared to the ranitidine group (p<0.01). Omeprazole treatment resulted in a significantly better score for the QoL-dimensions, swallow and eating problems (p=0.01) and reflux related problems (p=0.006).

Conclusion: These findings show that also in mild RO omeprazole 20 mg o.m. was clearly more efficacious on both symptomrelief and mucosal healing than ranitidine 300 mg norte. Furthermore, omeprazole generates a bigger improvement of the patients QoL than ranitidine.

SYMPTOMS ARE QUESTIONABLE INDICATORS OF THE SEVERITY OF GASTRO-oesophageal reflux: POST FUNDOPPLICATION

A Anggiatash, J Wang, SD Singh, WA Owen, AR Jones, WJ Owen
Department of Surgery, Guy's Hospital, London.

Between 1983 and 1993, 110 consecutive patients had a Nissen fundoplication (NF) for gastro-oesophageal reflux (GOR) disease.

Before NF patients' symptoms were assessed and patients tested: by Bernstein acid perfusion test (BAPT), standard oesophageal manometry to exclude patients with primary motility disorder, then ambulatory 24-hour oesophageal pH monitoring to confirm the presence of pathological GOR. Of the post-NF patients 15 (14%) continued to complain of GOR symptoms.

These 15 patients were re-assessed and all tests repeated over 4-72 months (mean: 19.3 month). Results: In 6 patients (40%) NF reduced reflux to zero and in another 6 patients (40%) reflux was reduced to a very low level (percentage of total reflux; median=1.2%). However in 3 patients (20%) pathological GOR persisted.

Percentage of patients with symptoms of:

Pre-NF

Post-NF

HB AR EP D

100% 40% 73% 7%

73% 20% 47% 20%

HB: heartburn; AR: acid regurgitation; EP: epigastric pain; D: dysphagia.

Post-operative results of BAPT in these 15 patients: sensitivity:0%; specificity:75%.

Conclusion: 1. After NF 86% of patients were relieved of GOR symptoms.

2. Of those who continued to complain 80% did not have pathological GOR on objective testing despite a suggestive history. 3. Post NF, BAPT proved to be an insensitive but specific test for identifying patients with GOR-related symptoms. 4. When symptoms persisted after NF objective testing for GOR is essential to have a clear cut diagnosis.

THE PRESENCE OF A CATHETER THROUGH LOWER OESOPHAGEAL SPHINCTER DOES NOT PROMOTE GASTRO-oesophageal reflux

A Anggiatash, G Taylor*, N Bright, J Wang, WA Owen, AR Jones, SD Singh, WJ Owen
Department of Surgery and Clinical Science*, Guy's Hospital, London.

To study lower oesophageal sphincter (LOS) function, a pressure-sensing device (PSD) (Gaeltec) positioned at the LOS was used. The aim was to examine the effect of the catheter through LOS on the induction of gastro-oesophageal reflux (GOR).

An ambulatory 24-hour oesophageal pH (Synectics) study was used to confirm the presence of pathological GOR (1st test) in 19 patients. This used an antimony pH sensor positioned 5 cm above the LOS as determined manometrically. The test was repeated (2nd test) using a catheter incorporating the PSD (positioned at LOS) bonded to another catheter with dual antimony pH sensors (combined diameter: 5mm), one at 5cm above the LOS and the other 15 cm below it. On both occasions, patients were instructed to avoid taking food and drink with pH < 4 and pursue normal daily activities.

The pattern of GOR at 5cm above the LOS on both tests (median) was as follows:

<table>
<thead>
<tr>
<th>Test</th>
<th>Total reflux (P)</th>
<th>Upright reflux (P)</th>
<th>Supine reflux (P)</th>
<th>Mean duration of reflux episode (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st test</td>
<td>8.8</td>
<td>9.7</td>
<td>5.3</td>
<td>3.8</td>
</tr>
<tr>
<td>2nd test</td>
<td>8.7</td>
<td>9.2</td>
<td>8.5</td>
<td>3.8</td>
</tr>
</tbody>
</table>

No significant difference was found in the above parameters between the 1st and 2nd test. The 2nd test failed to detect pathological GOR in 3 patients (15.7%).

Conclusion: Trans-LOS device with a diameter of 5mm does not promote GOR in patients with pathological GOR.
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REPRODUCIBILITY OF PERCEPTION TO OESOPHAGEAL DISTENSION
J.D. Barlow, D.G. Thompson
University of Manchester, Hope Hospital, Manchester U.K.

Background: Despite its increasing use as a diagnostic tool, the reproducibility of the perception responses to oesophageal distension and factors responsible for their quality remain uncertain.

Aims: To study the factors determining perception of oesophageal distension in the human proximal (somatic) and distal (visceral) oesophagus.

Methods: Fifteen subjects mean age 33 yrs, were studied using a 2cm inflatable balloon sized 3cm below the UOS for proximal, and 5cm above the LOS for distal studies. Inflation was increased in 1ml increments up to the maximum tolerated volume (MTV). A cross-modality scoring system was used to record perception intensity.

Protocol 1: Three stepwise distensions were conducted to determine reproducibility of threshold (MTV). Protocol 2: Distensions were conducted in random order to test for 'expectation effects'. Protocol 3: Distensions were conducted whilst the subject read aloud from a book to test for 'distraction effects'. Protocol 4. The balloon was inflated at frequencies of 1, 0.5 and 0.2 Hz to determine effect of repeat stimulation.

Results: Proximal oesophagus: Protocol 1: Thresholds during the successive runs were highly reproducible p<0.1. Protocol 2: Random inflation produced higher MTV than stepwise inflation (mean ± SEM) (14.57 ± 1.41 vs 12.81 ± 1.26) p<0.01. Protocol 3: Distraction increased both thresholds, T (8.6 ± 1.94 vs 5.31 ± 0.81) p<0.05, and MTV (15.6 ± 3.41 vs 12.81 ± 1.26) p<0.05. Protocol 4: Distension at 1, 0.5 and 0.2 Hz showed comparable thresholds (p>0.05). Distal Oesophagus: Comparable results to the proximal oesophagus were found but thresholds were consistently greater in the distal segment. Proximal vs distal differences were (T) (5.3 ± 0.81 vs 6.68 ± 0.82 p<0.01); (MTV) (12.81 ± 1.26 vs 17.43 ± 1.68 p<0.01).

Conclusions: Sensation from oesophageal distension is reliably and reproducibly perceived from both the proximal and distal oesophagus but with consistently different thresholds between the two regions. The presence of expectation and distraction effects indicate modulation by higher centres and need to be controlled for when conducting patient studies.

W30

OESOPHAGITIS IS COMMON IN PATIENTS WITH RHEUMATIC DISEASES AND IS INCREASED BY NSAIDS
MM Arnold, F. McKenna
(Introduced by WDW Rees)
Traford General Hospital, Manchester

Oesophagitis associated with non-steroidal anti-inflammatory drugs (NSAIDs) is infrequently reported. 405 patients attending a rheumatology outpatients' clinic were examined by a single endoscopist and oesophageal lesions graded 1 to 4. 101 of these were endoscoped before, and during treatment with NSAIDs. 261 patients (202 females) had rheumatoid arthritis (RA); 106 (72%) had oesophagitis (OA); 38 (18%) had other rheumatologically related conditions. 154 had not taken NSAIDs within 3 months of endoscopy; 351 patients were endoscoped on regular standard dose NSAIDs. Overall, oesophagitis was found in 17%.

Oesophagitis was present in 11.5% of patients not on NSAIDs compared with 20% taking NSAIDs (95% confidence intervals 1.06-2.78, p<0.05).

Gastric and duodenal ulcers were present in 70 patients (53 GU, 15 DU, & 2 with both GU + DU) in the NSAID group (43% asymptomatic) and in 8 (1 GU, 1 malignant GU, 6 DU) in the control group (50% asymptomatic). 70% of patients with oesophagitis had dyspeptic symptoms (p<0.001, NSAID group; p=0.0013 no NSAID group, x²).

We conclude that oesophagitis is common among patients with arthritis and that the incidence is increased by the use of NSAIDs. Oesophagitis is more commonly symptomatic than gastric-duodenal lesions associated with NSAIDs.

PNEUMATIC DILATATION FOR ACHALASIA: A META-ANALYSIS
A.H. Mohamed, G Tougas, R H Hunt
McMaster University, Hamilton, Ontario, Canada

Background: Pneumatic dilatation and surgical myotomy are traditional therapeutic options in the treatment of achalasia. Both procedures give favourable results, although surgery has better long-term success compared with earlier methods of dilatation. Different dilators have been used in achalasia, but recently balloon dilatation has been favoured. Our aim was to evaluate success with the various approaches to dilatation. Methods: A fully recursive Medline search identified 42 trials of pneumatic dilatation for achalasia between 1980 and 1993. Non-English and/or dual publications were excluded. Papers were reviewed by 2 reviewers and 1 arbiter resolved all discrepancies. 26 trials met strict entry criteria: i) manometric and radiologic diagnosis ii) endoscopy to exclude secondary causes iii) follow-up after 6 months.

Results:

<table>
<thead>
<tr>
<th>Dilator</th>
<th>t</th>
<th>n</th>
<th>imp (%)</th>
<th>sub dil (%)</th>
<th>perf (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slurry</td>
<td>2</td>
<td>450</td>
<td>342 (70%)</td>
<td>47 (10%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>Wincoll</td>
<td>1</td>
<td>45</td>
<td>35 (78%)</td>
<td>5 (11%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Mosher</td>
<td>3</td>
<td>106</td>
<td>62 (58%)</td>
<td>15 (14%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Rider Moller</td>
<td>6</td>
<td>327</td>
<td>209 (64%)</td>
<td>94 (36%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Brown Mc Iard</td>
<td>5</td>
<td>274</td>
<td>179 (65%)</td>
<td>62 (23%)</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>Rigiflex</td>
<td>7</td>
<td>176</td>
<td>151 (86%)</td>
<td>24 (21%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>87</td>
<td>77 (88%)</td>
<td>16 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>1465</td>
<td>1055(72%)</td>
<td>263 (20%)</td>
<td>53(4%)</td>
</tr>
</tbody>
</table>

imp=improved sub dil=subsequent dilatation perf=perfusion

Conclusion: Rigiflex balloon dilatation achieves high initial success (86%), requires infrequent subsequent balloon dilatations (20%) and has low perforation rates (0%), coupled with an economic benefit over surgery. This favours initial treatment with pneumatic dilatation.

Multicentre, controlled, prospective, randomised trials with large numbers will be needed to compare directly balloon dilatation with newer methods such as botulism toxin injection and laparoscopic myotomy for the treatment of achalasia.
ADVERSE HEPATO-PULMONARY INTERACTION IN CYSTIC FIBROSIS - A MECHANISM FOR INCREASED MORTALITY?
S.G.J. Williams, J. Samsays, J. A. Innes, A. Guz, D. Westaby
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To evaluate a possible interaction between hepatic and pulmonary disease with respect to haemodynamic changes 45 consecutive patients with CF (22 with liver disease) underwent non-invasive measurement of cardiac output, heart rate and blood pressure at rest. CF biliary cirrhosis was defined using clinical (hepatomegaly and/or splenomegaly), biochemical and ultrasound criteria (abnormalities of liver parenchyma and edge and perilobar fibrosis) in the absence of other causes of chronic liver disease. 16 of the liver disease group were Child-Pugh grade A and 6 grade B. Simple regression analysis, using lung function (percentage predicted FEV1 (%FEV1)) as the independent variable, was performed on the two groups ('liver' and 'non-liver'). In the group of patients without liver disease, tachycardia correlated with %FEV1 (r=0.44, p<0.05), but there was no correlation with other haemodynamic variables. In the group with CF related biliary cirrhosis, correlations were found between deteriorating pulmonary function and heart rate (r=0.47, p<0.05), cardiac index (r=0.48, p<0.05) and systemic vascular resistance index (r=0.42, p<0.05). These results suggest an additive effect of deteriorating pulmonary function on the severity of the covert haemodynamic changes documented in CF liver disease. Increased haemodynamic stresses in the CF patient with liver disease and deteriorating pulmonary function, an association not observed in the cohort without liver disease, may be an explanation for premature cardio-pulmonary mortality in this sub-group of patients.

Liver

ATP DILATES THE HEPATIC ARTERY VIA P1-PURINOCPTORS
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Adenosine is partly responsible for the generation of the buffer response, the hepatic arterial hyperemic response to a reduction in portal venous flow, and it has been suggested that adenosine 5'-monophosphate (ATP) is also involved (Matthie and Alexander, 1990). ATP is a potent vasodilator of the hepatic arterial vascular bed. It has previously been shown that this action occurs by stimulation of P1-purinoceptors on the hepatic arterial endothelium releasing nitric oxide (Matthie et al., 1991). However, in some vascular beds ATP may also act via adenosine P1-purinoceptors to elicit vasodilation (Kennedy and Burnstock, 1985). In this study, by using the P1-purinoceptor antagonist 8-phenyltheophylline, we have investigated whether a proportion of the HA vasodilation to ATP is due to the breakdown of ATP to adenosine in the liver.

The model used in these experiments was the isolated dual-perfused rabbit liver (Alexander et al., 1992). The livers (wt. 98.6 ± 6.4g) of 12 New Zealand white rabbits (wt. 2.7 ± 0.2kg) were perfused with Krebs' buffer solution, at 37°C, at flow rates of 25 and 75 ml min⁻¹ 100g⁻¹ liver⁻¹ via the hepatic artery and portal vein respectively. The vascular tone of the preparation was raised by the addition of 10⁻³-10⁻⁴M methoxamine to give perfusion pressures of 153 ± 5.7 and 1.7 ± 0.4 mmHg for the hepatic arterial and portal venous vascular bed respectively. The hepatic arterial vasodilator responses to bolus intra-arterial injection of ATP (n=6) were inhibited by 10⁻⁶M 8-phenyltheophylline (logED50 8.7 ± 0.2 to 7.6 ± 0.3, p<0.001, Student's paired t-test). Similar results were obtained following intra-portal injection of ATP (n=6) although the maximal arterial response was not attained.

This work indicates that a significant proportion of the hepatic arterial vasodilation to ATP is due to the breakdown of ATP to adenosine resulting in action on P1-purinoceptors. This action of ATP on the hepatic artery is consistent with the putative role of ATP in the generation of the buffer response.


W33

OESOPHAGEAL ISCHEMIA IN UNEXPLAINED CHEST PAIN
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We have previously reported evidence of oesophageal ischaemia in patients with oesophageal dysmotility associated with unexplained chest pain. Using a 50mA, 7 degrees Celsius, cold water challenge, we found that such patients had abnormally slow rewarming rates. We have now studied 32 patients in whom standard diagnostic oesophageal manometry was normal. 20 of these patients had coronary angiograms, which were normal. 15 of these patients had thallium myocardial perfusion scans of which 10 were abnormal. The mean rewarming time-constant, after cold challenge, in the 22 patients, 73 sec, (standard deviation: 12 sec), was significantly longer compared to 23 normal controls, 45 sec (SD 10sec) (p<0.001). Additionally in the patient group the rewarming in the mid oesophagus when compared to the lower oesophagus was significantly slower. Mid oesophagus: mean 79sec. Lower oesophagus: mean 67 sec (p<0.001, paired t test). These slower rewarming rates are in keeping with reduced oesophageal blood flow.

We conclude that
1) some patients with unexplained chest pain have oesophageal ischaemia without overt oesophageal dysmotility.
2) A microvascular disorder may account for the coexistence of oesophageal and myocardial perfusion abnormalities.
3) The mid oesophagus is more ischaemic than the lower oesophagus in these patients.


W34

THE INCIDENCE AND MANAGEMENT OF LASER ASSOCIATED OESOPHAGEAL PERFORATION
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Department of Surgery, Guy's Hospital, London, SE1 9RT

Laser oesophagoscopy is effective in palliating malignant dysphagia. Nevertheless, the possibility of iatrogenic perforation is a source of concern. Over the last 4 years we have treated 350 patients with irresectable lower or middle third oesophageal cancers. They have required 1257 treatment episodes (0-10 per patient). On 424 occasions lasering has been preceded by wire-guided dilatation (0-7 per patient). A total of 25 perforations were recognised in 22 patients (6% of patients; 25% of treatments). Twenty-three perforations were recognised following dilatation and prior to lasering (5% of dilatations). All of these were managed non-operatively - nil by mouth, IV hydration, antibiotics and H2 receptor blockade - until oesophageal healing was documented by contrast swallow. This group suffered 3 deaths (13%). Two perforations were not recognised at endoscopy, and are therefore attributed to the laser. Both were clinically evident (peritonitis) within 12 hours, but both patients died. We conclude that oesophageal perforation occurring during palliative laser oesophagoscopy is rarely a consequence of lasering per se. Furthermore, perforation of oesophageal lesions during dilatation is uncommon. When the former occurs, it is recognised late and likely to prove fatal. By contrast, the latter is endoscopically recognisable and can be successfully treated by the early institution of non-operative measures.
CYTOKINE PROFILE IN AUTO-IMMUNE LIVER DISEASES USING THE REVERSE HAEMOPLASTIC PLASMA ASSAY.

ERG Martens, CE Lewis, KA Fleming, RW Chapman, Dept of Gastroenterology and Nuffield Dept of Pathology, John Radcliffe Hospital, Oxford. OX3 9DU.

The Th1 group of cytokines - interferon gamma (IFN-γ), tumour necrosis factor alpha and beta (TNF-α and TNF-β) and interleukin-2 (IL-2) - is associated with cell mediated immune response. T-cell mediated cytotoxicity is believed to play an important role in the liver damage in primary sclerosing cholangitis (PSC), auto-immune chronic active hepatitis (AIH) and primary biliary cirrhosis (PBC). AIH: To investigate the cytokine profile of the peripheral blood lymphocytes in PSC, PBC and AIH. Materials and methods: Fresh peripheral blood mononuclear cells were obtained by gradient centrifugation from 10 patients with PSC, 6 PBC, 5 treated AIH, 4 alcoholic liver disease (ALD) and 3 healthy volunteers. The secretion of IFN-γ, TNF-α, TNF-β and IL-2 was analysed using the reverse haemolytic plaque assay. Briefly the cell suspension was incubated on a monolayer of protein-A conjugated sheep erythrocytes with the appropriate polyclonal anti-cytokine serum. The reaction was developed using complement and a ring of haemolysis was formed around the cytokine producing cells, allowing the assessment of cytokine production at the single cell level. Results: In PSC 5/10 patients had detectable IFN-γ secretion, 1/10 had detectable IL-2 secretion and 1/10 had detectable TNF-α secretion. The patients that secreted IL-2 and TNF-α also secreted IFN-γ. No cytokine secretion was detected in patients with AIH, PBC and healthy volunteers. In ALD, 2/4 patients secreted TNF-α, 3/4 secreted IL-2, 1/4 secreted TNF-β and no secretion of IFN-γ was detected. The patients that secreted TNF-α and IL-2 also secreted TNF-β. Conclusion: These results suggest that in PSC there is up-regulation of the pro-inflammatory cytokine IFN-γ suggesting a Th1 cytokine profile, in contrast with PBC where there is down-regulation of the Th1 group of cytokines. The negative results from AIH could be due to steroid treatment.

ROLE OF NEUTROPHIL ACTIVATION IN REPERFUSION INJURY FOLLOWING LIVER TRANSPLANT

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Scottish Liver Transplant Unit, Dept of Medicine and Blood Transfusion Service, Royal Infirmary, Edinburgh.

Reperfusion injury has been implicated in the development of primary graft dysfunction after orthotopic liver transplantation (OLT). Neutrophil migration and activation may be involved in the pathogenesis of this injury.

We studied neutrophil activation by measuring neutrophil elastase (NE) by radioimmunoassay, in serial blood samples of 11 patients pre-transplant, during anephaptic phase, and postreperfusion at 30 min, 1, 2, 6, 9, and 24hrs.

Results: Pre-transplant NE was significantly raised (39.815.6ng/L, mean±SEM, n=9) compared with controls (18.7±10.1ng/L, p<0.01, n=11). Following reperfusion NE levels increased markedly reaching a maximum at 9 hours (458.5±129.4ng/L, p<0.001, n=10). This was followed by a fall but remained significantly high at 24 hrs (365.5±109.6ng/L, p<0.001, n=10). The changes in NE after reperfusion correlated with markers of graft function e.g. time to normalization of prothrombin time (r=0.5, p<0.03) and correction of acidosis (r=0.787, p<0.002).

Conclusion: The results of this study indicate that marked neutrophil activation occurs in relation to reperfusion during OLT, and the changes of NE correlated with markers of graft function, suggesting that neutrophil activation plays a role in reperfusion Injury post transplant.

SOLUBLE ADHESION MOLECULES AND CYTOKINES IN AUTOIMMUNE CHRONIC ACTIVE HEPATITIS (AIACH)

K J Simpson, A L Jones, J F Dillon, F A D Boucher, P C Hayes
Liver Research Laboratories, Department of Medicine, Royal Infirmary, Edinburgh.

Introduction: Soluble adhesion molecules are increased in inflammatory liver disease, including AIACH. However the in vivo stimulus to their release is unknown although in vitro studies implicate intestinal IL-1, IL-4, IL-6, tumour necrosis factor (TNF) and interferon(IFN)-γ. Methods: ELISA was used to measure the soluble adhesion molecules ICAM-1, E-selectin and VCAM-1 and IL-1β, IL-4, IL-6, TNF-α and IFN-γ in 27 patients with AIACH and 10 controls, IL-1β, IL-4, IL-6, and IL-8R by reverse transcription (RT)-PCR. soluble IL-6 receptor (IL-6R) levels were also measured. For the purposes of analysis the AIACH patients were defined as active (ALT>100) or inactive (ALT<50). Results: Levels of IL-1β, IL-4 and IFN-γ were undetectable in all subjects. Levels of TNF-α were similar in controls (2.6±1.7pg/ml, mean±SEM) and patients with inactive (3.3±1.6, N=17) or active (3.6±1.8, N=11) AIACH. IL-6 was detected in only 1 control (1.5pg/ml) but most patients with AIACH, whether active (7.65±2.1, N=10) or inactive (6.34±2.7, N=14). Circulating IL-6 was similar in all groups, but IL-6R was significantly increased in patients with active (319.8±133.7ng/ml, N=11, p<0.01) or inactive (227±41.8, N=12, p<0.05) AIACH compared with controls (162.0±51.5). Soluble ICAM-1, E-selectin and VCAM-1 were significantly increased (p<0.05) in patients with AIACH compared with controls. No significant correlations (p>0.01) were noted between the levels of soluble adhesion molecules and the detectable cytokines although IL-6R was correlated with ICAM-1 (r=0.628) and E-selectin (r=0.577). Conclusions: Soluble adhesion molecules, IL-6 and IL-6R levels are increased in patients with AIACH, however the results do not explain the underlying stimulus to the increased soluble adhesion molecules observed.

TIPS: PALMAZ OR WALL STENTS?

R Jalan, K J Simpson, D N Redhead, P C Hayes Centre for Liver & Digestive Diseases, Department of Medicine & Radiology, Royal Infirmary, Edinburgh.

TIPS is a relatively new technique for treating bleeding from oesophageal varices, portal gastropathy and resistant ascites. The aim of this study was to compare the two stents most commonly used Palmaz (PS) (Johnson and Johnson) and Wall stents (WS) (Schneider).

Patients & Methods: PS was inserted in the first 7/4 and WS in the subsequent 26 patients undergoing TIPS over a 2 year period. Both groups were well matched for age, sex, aetiology, severity of liver disease and the prov TIPS portal pressure gradient. Indications were acute or uncontrolled variceal bleeding - 12 (WS - 8, PS - 4), recurrent variceal bleeding - 27 (WS - 12, PS - 15), resistant ascites - 5 (WS - 2, PS - 3) and others - 6 (WS - 1, PS - 5).

Results: Patients with PS and WS have been followed up for 15 and 9 patient years respectively. Over this period 17 patients have died (PS - 7, WS - 10) and 8 have been retransplanted (PS - 6, WS - 2). Mean shunt size for PS and WS were 12.1 and 12.6 mm respectively. Mean post TIPS PVP was 12.2 for PS and 8.3 mmHg for WS, (p < 0.01). Mean number of PS and WS required were 2.79 (SD - 0.61) and 1.3 (SD - 0.4) (p<0.01) respectively. Variceal bleeding occurred in 10 patients (PS - 7, WS - 3, p<0.01). Shunt complications were less common with WS than PS (18 vs 1), 1.2 vs 5.5 events per patient year) and included portal vein thrombosis - 2 (PS - 2), shunt thrombosis - 2 (PS - 1, WS - 1), migrated stent - 2 (PS, intraluminal hyperplasia - 1 (PS - 1, WS - 3, p<0.01), and asymptomatic subcutaneous vein thrombosis - 2 (PS - 4, WS - 1). Balloon dilatation for intraluminal hyperplasia in patients with PS was associated with complications such as rupture of the balloon (7 patients) and balloon impaction (2 patients).

Conclusions: The results of this study indicate that PS are 1. Cheaper (fewer required per shunt) 2. More effective (lowering PVP). 3. Associated with fewer clinical and stent related complications and should therefore be considered the stent of choice for TIPS. Long term follow-up is necessary.
THE MECHANISM OF THE AUTONOMIC NEUROPATHY OF CIRRHOSIS.

J F Dillon, J M M Neilson, I A D Boucicier, P C Hayes

LIVER RESEARCH LABORATORIES, DEPARTMENTS OF MEDICINE AND MEDICAL PHYSICS ROYAL INFIRMARY OF EDINBURGH

INTRODUCTION:
Vagal dysfunction is reported in 50-70% of patients with cirrhosis, irrespective of aetiology, detected by cardiovascular reflex tests. We have previously shown that RR-variability on 24 hour ECG is a sensitive marker of Vagal dysfunction. Angiotensin II inhibits vagal function in animals and it is elevated in cirrhosis.

AIM:
To observe the effect of Captopril on vagal dysfunction in cirrhosis.

METHODS:
6 patients with cirrhosis (biopsy proven, Childs A, B, C: mean age 50) and vagal dysfunction detected by 24 hour ECG were treated with Captopril 25mg, t.d.s. for 48-hours. The 24th hour ECG was then repeated on therapy.

RESULTS:
Mean RR remained unchanged baseline 89.8±4.6mmHg (mean±SEM) versus 91.8±5.2mmHg after treatment. Mean baseline RR-variability was 632±270 counts/24hours and it increased in all patients, with Captopril, to 1212±230 p<0.0006. Three increased into the normal range.

CONCLUSION:
The vagal dysfunction of cirrhosis is caused by neuroendocrine by Angiotensin II and is not due to a neuropathy.

SALIVARY IMMUNOGLOBULINS AS DIAGNOSTIC MARKERS OF PREVIOUS HEPATITIS A INFECTION.


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**Dept. of Medicine and Gastroenterology, Royal College of Surgeons in Ireland, and Beaumont Hospital, Dublin, Ireland.

The usefulness of salivary immunoglobulin (Ig) in the determination of immunity to Hepatitis A (HAV) infection has been investigated. With improving hygiene the prevalence of childhood Hepatitis A is decreasing, giving rise to an increasing proportion of non-immune adults. We wanted to determine if Hepatitis A virus (HAV) can be detected by large scale vaccination of populations arises. Vaccination of entire populations is unlikely to be cost effective, so a simple, quick method of determination of previous immunity will become necessary. The determination of anti-HAV total Ig (primarily IgG) levels in saliva is the easiest and safest method. Saliva acquisition is more simple than venepuncture, is painless and non-invasive, and the sample itself presents less danger to those handling it than does blood.

A competitive Enzyme Linked Immunosorbent Assay (ELISA) for Total Salivary anti-HAV Ig has been developed. Saliva and serum were obtained from 205 apparently healthy volunteers and tested for anti-HAV total Ig. The study was blinded by assigning each saliva a random number, and the true identity of the samples was not revealed until after testing was complete. Of the 205 sera tested, 74 were anti-HAV Ig positive. 70 of the paired salivas to these samples were also positive in the assay, with 4 false negatives and no false positives. The assay therefore exhibited a sensitivity of 94.6%, and a specificity of 100%.

We conclude therefore that saliva has the potential for use in place of serum in the determination of previous infection with HAV. Salivary testing has the potential to greatly reduce the cost of vaccination schemes, as it makes possible the quick and easy screening of large numbers of individuals, thereby eliminating the immune population from the vaccination programme.

HLA-G POLYMORPHISM IN HEREDITARY HAEMOCHROMATOSIS

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It is established that the Hereditary haemochromatosis (HH) gene is closely linked to HLA-A but studies to date using probes for HLA-A, B, C and E have failed to show any characteristic Restriction fragment length polymorphism (RFLP) pattern in HH. In the MHC Class I region there are at least 18 genes including HLA-G, one or more of these could be adjacent to this gene. The aim of this study was to analyse RFLP pattern in HH using HLA-G Specific probe 23.2d.

RESULTS:
Patients and Methods: HH was diagnosed using standard diagnostic criteria. Ten HH typed HH patients and 10 HLA typed controls (normal iron studies) were included. DNA was extracted and digested with EcoR1 enzyme and subjected to Southern blotting and hybridisation. RFLPs were detected by using autoradiography at ~80C.

Results: The HLA-G specific probe 23.2d detected 6 EcoR1 fragments in the 10 controls. The 6th and the smallest EcoR1 fragment was not detected in 9 of the 10 HH patients.

CONCLUSION: HLA-G Specific probe detects an EcoRI fragment in control subjects which is absent in major or all HH patients. Since HLA-G is expressed only in extraembryonic trophoblasts it is unlikely to be implicated in pathogenesis of HH. Our results, however, suggest that the HH gene is at a site either between HLA-A and HLA-G or telomeric to HLA-G.

RECOGNITION OF HEPATITIS C COMPPLICATING ALCOHOLIC LIVER DISEASE

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The aim of the study was to look at the liver biopsies of alcoholics to identify those features which point to co-existent hepatitis C infection. Fifty alcoholics were tested for hepatitis C virus (HCV) using PCR amplification. The biopsies were then examined by an experienced pathologist unaware of the hepatitis C status of the patient. 8 Patients were hepatitis C virus positive,13% of these were cirrhotic,47% were hepatitis C negative. 36% of these were cirrhotic. Features identified in the biopsies, together with the sensitivities (SI) and specificities (SP) and signficance levels (P values) are listed below:

<table>
<thead>
<tr>
<th>Feature</th>
<th>C+VE No.(%)</th>
<th>C-VE No.(%)</th>
<th>SI %</th>
<th>SP %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes in portal tracts</td>
<td>3(38)</td>
<td>19(40)</td>
<td>38</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphoid aggregates in portal tracts</td>
<td>5(63)</td>
<td>0(0)</td>
<td>68</td>
<td>100</td>
<td>0.00032</td>
</tr>
<tr>
<td>Lymphocytes in the lobules</td>
<td>5(63)</td>
<td>1(2)</td>
<td>62</td>
<td>98</td>
<td>0.00018</td>
</tr>
<tr>
<td>Apoptotic hepatocytes</td>
<td>20(25)</td>
<td>0(0)</td>
<td>75</td>
<td>100</td>
<td>0.008</td>
</tr>
<tr>
<td>Fibrosis spurring pattern</td>
<td>6(75)</td>
<td>2(4)</td>
<td>75</td>
<td>96</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

In conclusion those features found to be most useful in identifying coexistent hepatitis C infection pathologically were found to be the presence of lymphoid aggregates in the triads, and in the lobules as well as the pattern of fibrosis- notably sparing rather than perivenular fibrosis.

In conclusion those features found to be most useful in identifying coexistent hepatitis C infection pathologically were found to be the presence of lymphoid aggregates in the triads, and in the lobules as well as the pattern of fibrosis- notably sparing rather than perivenular fibrosis.
FOETAL MORTALITY ASSOCIATED WITH CHOLESTASIS OF PREGNANCY AND THE POTENTIAL BENEFIT OF THERAPY WITH URSODEOXYCHOLIC ACID

M H Davies, R C M A da Silva, J B Weaver and E Elias
Birmingham Liver Unit and Birmingham Maternity Hospital, Edgbaston, Birmingham

Cholestasis of pregnancy (COP) is frequently considered a benign condition. We present reports of 7 females with previous COP referred during the past 12 months. We also present outcome of three cases referred during pregnancy who received ursodeoxycholic acid.

COP affected eleven previous pregnancies in these 7 mothers. Ten of the eleven pregnancies were managed expectantly and were associated with perinatal morbidity or mortality. There were eight stillbirths, a premature delivery with foetal distress and an emergency Caesarean section for foetal distress. The eleventh pregnancy, was managed actively and delivery was without complication.

Three women became pregnant again and were referred during pregnancy. In each, COP developed in the third trimester, with severe pruritus, gross elevation of serum bile acids and deranged liver function tests. In each case, ursodeoxycholic acid was prescribed with fully informed patient consent. Therapy was associated with rapid clinical improvement and resolution of deranged biochemistry. Delivery was induced in each case. All babies were born alive and well.

Conclusions:
1) COP is associated with significant foetal morbidity and mortality, yet continues to be managed expectantly, despite evidence in favour of active management.
2) Appropriate obstetric care presents a potential means of reducing perinatal mortality.
3) Ursodeoxycholic acid appears safe, effective therapy for cholestasis of pregnancy.

EMERGENCY TIPS AS SALVAGE TREATMENT FOR UNCONTROLLED VARICEAL BLEEDING. PA McCormick, R Dick, EB Faneagou, JCT Chin, L Greenslade, N McIntyre, AK Burroughs, University Dept. of Medicine, Royal Free Hospital, LONDON UK

The role of TIPS in the management of portal hypertension is not yet clear. We report our experience with TIPS as an emergency salvage treatment in patients with variceal bleeding refractory to standard medical and endoscopic treatment. Over a 2 year period 221 episodes of variceal bleeding were treated in the liver unit and emergency TIPS was performed on 17 occasions for patients with uncontrolled bleeding (Pugh class: uncontrolled A2, B7, C9: 53% alcoholic cirrhosis). The procedure was technically successful in all patients. Variceal bleeding was controlled in 15/17, of whom required a second TIPS procedure because of early rebleeding. The mean portosystemic pressure gradient decreased from 29 to 15 mmHg. Eight patients died. One from intra-abdominal haemorrhage one day after TIPS; 6 within 20 days of liver failure and sepsis and one at 60 days after emergency cholecystectomy. The mean follow up of the surviving 9 patients was 10 months (range 1-15 months). The shunt was occluded in 3 of 9 patients within 2 months with subsequent recurrent bleeding in 2. Both had a new stent inserted which blocked within 6 months and both underwent a portacaval shunt. Two other patients had a successful liver transplant (one for recurrent bleeding and another for refractory ascites and encephalopathy). All 9 surviving patients are alive and well.

CONCLUSIONS: 1) TIPS is an effective therapeutic option in patients with acute variceal bleeding in whom sclerotherapy and other medical treatments have failed. 2) Despite successful TIPS, in-hospital mortality was 41% in this patient group, reflecting the severity of the underlying liver disease.

PERCUTANEOUS LIVER BIOPSY - THE INFLUENCE OF CLOTTING STATUS AND ULTRASOUND GUIDANCE ON COMPLICATION RATE

Dr EJ Roach, Dr DB Jones, Dr MC Ng. Dept Gastroenterology - Concord Hospital, Sydney, Australia

Liver biopsy is accepted as a diagnostic tool in the diagnosis of liver disease. A trend towards ultrasound guided biopsies is apparent, probably due to improved availability and potential advantages.

Between 1986 and 1991, 275 patients (age range 15 to 77; male=180) underwent percutaneous liver biopsy (fine needle aspiration biopsies were excluded). Indications, diagnoses, biopsy technique and needle type, coagulation profile and complications were documented retrospectively. Biopsy techniques included True-Cut(T)(20), Biopsy Gun(B)(32), Menghini(M)(89), ultrasound-guided(U/S)(121) and unknown(13).

One hundred forty patients were day cases, 112 were already inpatients, 16 were overnight admissions (7 were unknown). The commonest indications were abnormal LFTs, abnormal iron chemistry and hepatomegaly. There were six major complications, all due to haemorrhage requiring blood transfusion (2 to 10 units). Five of these were already inpatients and one was an overnight admission. Two of these patients died and two required surgery. Four of the six (60%) had abnormal coagulation (1), low platelet count (2) or both (1). Of the two hundred sixty nine patients without major complications forty five (17%) had abnormal clotting parameters. No biopsy technique was free of major complications (T=2, B=1, M=1, U/S=2). There were 50 minor complications, most of which were local and shoulder-tip pain. These were not influenced by clotting status or US guidance. The presence of local pain did not predict subsequent major complications. Eight of the day case patients subsequently required overnight admission because of minor complications. All were discharged within one to two days without sequelae.

CONCLUSIONS: 1) Mortality of liver biopsy over five years was 0.7%. Major complications occurred in 2% and minor complications in 18% of patients. 2) The risk of major complication is significantly increased when there is abnormal clotting. 3) In a selected group of patients the procedure can be carried out safely as a day case. 4) Ultrasound guidance did not seem to influence the complication rate.

TEMPORARY HETEROTOPIC AUXILIARY LIVER TRANSPLANTATION FOR FULMINANT HEPATITIS B


Depts. of Gastroenterology & Hepatology, Surgery, Virology, Nuclear Medicine, Pathology, and Anesthesiology, University Hospital Leiden & Dept. of Internal Medicine, Diaconess Hospital Eindhoven, The Netherlands

BACKGROUND: Orthotopic liver transplantation (OLT) has been shown to improve survival in fulminant hepatic failure (FHF). However, after OLT life-long immunosuppression is necessary and graft complications may occur.

METHODS: We employed heterotopic auxiliary liver transplantation (HALT) in a 26-year old man with FHF due to hepatitis B virus (HBV) infection.

RESULTS: From a comatose state with seizures and decompensated posturing, the patient woke up the day after HALT. Despite HBV-recurrence the graft functioned sufficiently. After 2 weeks, when pentonitis developed, immunosuppression was stopped since the native liver was recovering as shown by serial HIDA scans, liver biopsies, clotting parameters and serum bilirubin. When severe rejection of the graft developed 2 weeks later, and the pentonitis had been treated successfully, the native liver had recovered sufficiently to allow the graft to be removed. The patient now, more than 6 months after HALT, is free from medication, is immune for HBV, his liver tests have returned to normal and he has regained his normal life.

CONCLUSION: Temporary heterotopic auxiliary liver transplantation for fulminant hepatitis B is feasible.
W50

Department of Surgery, Royal Liverpool University Hospital, Liverpool, U.K.

Nitrates have been reported to improve the efficacy of vasopressin in controlling variceal bleeding. Since there is a paucity of data on the haemodynamic effects of such combinations in severe hypovolaemia, we have undertaken such a study in portal hypertensive rats.

Portal hypertensive rats (partial portal vein ligation) were bled at a constant rate until the systolic blood pressure was 50 mm Hg. After a period of stabilisation groups of rats received continuous infusions of vasopressin (0.84U/g/h), isorhde mononitrate (10ug/kg/min) or a combination of vasopressin and isorhde or saline. Portal pressure and arterial blood pressure were measured continuously and collateral blood flow (consecutive intrasplenic injection of 99mTc-methylene diphosphonate and 99mTc-albumin microspheres) every 5 min throughout the study.

Haemorrhage decreased portal pressure but increased collateral blood flow in all four groups of rats (p < 0.001 ANOVA). Administration of vasopressin, saline or a combination of isorhde and vasopressin had no effect on portal pressure or collateral blood flow during hypovolaemia. In contrast, isorhde alone increased portal pressure (6.5 +/- 0.4 to 8.3 +/- 0.4 mm Hg; p < 0.02) but decreased collateral blood flow (62.0 +/- 14.5 to 34.5 +/- 10.9; p < 0.02) in hypovolaemic rats.

Since the efficacy of vasoactive drugs in controlling variceal bleeding depends upon their ability to reduce collateral blood flow, isorhde alone would appear to be more effective than either vasopressin alone or combination therapy during hypovolaemia.

W51

THE EFFECTS OF OCTREOTIDE ON HEPATIC ENERGY METABOLISM IN PORTAL HYPERTENSION. T. Munakata, B.R. Griffiths, P.A. Martin, R. Shields*, R.M. Edwards & S.A. Jenkins*
Magnetic Resonance Centre and Department of Surgery, University of Liverpool, Liverpool, U.K.

Recent observations suggest that octreotide is a safe and relatively effective treatment for the control of acute variceal bleeding. Since octreotide reduces liver flow, concern exists that it may further compromise liver function, particularly in patients with severe hepatic disease. Therefore the aim of this study was to investigate the effects of octreotide on hepatic energy metabolism in portal hypertensive patients using 31P Magnetic Resonance Spectroscopy (MRS).

Six portal hypertensive patients (Child's C; 2; Child's B, 4) underwent MRS after a 12h fast using a 1.5 Tesla GE Signa system with an 8cm surface coil. A 31PMR spectrum was obtained before and after a 20 minute infusion of octreotide (50 µg/h).

The baseline spectrum showed an enlarged P Extra peak consistent with previous observations in the cirrhotic liver. Octreotide infusion resulted in a significant decrease in circulating insulin levels (18.3 +/- 9.1 to 6.5 +/- 3.6 m U/l) but no changes in blood glucose. Furthermore, octreotide infusion did not result in any significant change in hepatic energy metabolites (PME 7.50 +/- 0.98 to 9.72 +/- 2.21; Pi 10.01 +/- 2.4 to 9.55 +/- 1.49; PDE 32.7 +/- 3.65 to 31.51 +/- 5.8; B-ATP 14.28 +/- 1.94 to 14.13 +/- 1.34).

The results of this study suggest that the alterations in liver blood flow elicited by octreotide do not comprises hepatic energy metabolism in portal hypertensive patients.

W52

DO ALTERATIONS IN THE RATE OF GASTRIC EMPTYING (GE) CONTRIBUTE TO THE PATHOGENESIS OF PORTAL HYPERTENSIVE GASTROPATHY (PHG)?
J.K. Balas, B.J. Grim, R. Sutton, A.T. Jones, Y. Yiannakou, R. Critchley and S.A. Jenkins
Departments of Nuclear Medicine, Surgery, Clinical Chemistry and Gastroenterology, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP.

There is little data on gastric emptying (GE) in cirrhotic patients and even less on those with PHG. Possibly, a delay in the rate of GE, by exposing the stomach to the deleterious effects of acid and pepsin, may contribute to the pathogenesis of PHG. Therefore the aim of this study was to evaluate the severity of PHG and GE in 50 patients with biopsy proven cirrhosis of differing aetiology, 37 of whom had oesophageal varices.

Two days after an upper gastrointestinal endoscopy all patients underwent GE studies using a semi-soliguid meal consisting of porridge labelled with 10 MBq of 18F-fluorodeoxyglucose (FDG)-labelled bran, two cheese sandwiches and a cup of tea. After appropriate corrections, the rate of GE was calculated from the area under the corrected time-activity curve.

Ten patients had severe (20%) and 25 (50%) mild PHG. The gastric mucosa appeared normal in 15 patients (30%). Although cirrhotics with severe PHG had a smaller area under the curve (3923.25; 2556.15 to 6224.01, median range) than patients with mild PHG (4232.88; 2540.89 - 6141.43) or no cirrhosis (2640.99; 2480.85 - 5986.02), the difference between the groups was not statistically significant (p = 0.24; Kruskal-Wallis H = 2.79, 2F).

Seven patients with oesophageal varices had a faster rate of GE than those with cirrhosis only (p = 0.01; Mann Whitney).

The results of this study indicate that GE of semi-solids in patients with oesophageal varices is more rapid than in cirrhotics without varices. Furthermore, there was no obvious relationship between the severity of PHG and GE. These observations suggest that alterations in GE are not involved in the pathogenesis of PHG.
**MONOCLONAL ANTIBODIES AGAINST MAJOR BASIC PROTEIN (BMK-13) AND EOSINOPHIL CATIONIC PROTEIN (EG2) FOR QUANTIFYING EOSINOPHILS IN HUMAN HEPATIC ALLOGRAFT REJECTION.** Z Ben-Ari, 1 A Dhillon, 1 A Lane, 1 R Moobbel, 1 K Rolles, 1 A Burgos, 2 A Whitmore, 2 Dept. of Histopathology, Royal Free Hospital 1 Dept. of Allergy and Clinical Immunology, National Heart and Lung Institute; London

Liver allograft histology is the standard diagnostic method for acute cellular rejection. Only one group has used EG2 for staining of an eosinophil cationic protein (ECP), concluding that eosinophils are a specific diagnostic feature for acute cellular rejection. However, the reliability of counting eosinophils on H&E sections has not been evaluated before. We quantified eosinophils in 17, day 5 protocol liver biopsies (12 patients). Rejection was diagnosed and graded histologically with clinical and biochemical correlation. 6 patients with CMV infection and 5 patients in whom the cause of the liver dysfunction was obscure served as controls. Eosinophil count was assessed by H&E and specific monoclonal antibody staining (1) EG2 (anti ECP) only for activated eosinophils, (2) BMK-13 (anti MBP-the major basic protein which has cytotoxic properties), a pan-eosinophilic marker. The average percentage of eosinophils of the total inflammatory infiltrate in portal tracts was 9% in the moderate to severe rejection group as compared to 0.25% in the mild rejection group (p<0.001) and 0% in the control groups (p<0.001). The H&E staining correlated with the BMK-13 positive cells, but these were more numerous than with H&E, and than with EG2 (p<0.01). This study confirms that eosinophils (activated and total) are a specific feature of acute cellular rejection, and are an aid to its diagnosis. BMK-13 is a useful pan-eosinophilic marker which is easier to count compared to H&E. The possible role of activated eosinophil as an effector cell in acute cellular rejection needs further study.

**Pancreas W54–W57**

**W54**

**IS PLASMA OSMOLARITY RAISED IN SEVERE ACUTE PANCREATITIS?** A.K.BANERJEE, R.JAIN, L.COOPE and T.M.BALFOUR Dept. of Surgery, Queen’s Medical Centre, Nottingham NG7

The pathogenesis and prediction of severe acute pancreatitis is uncertain. Previous work has shown that raised osmolality of ERCP contrast media, and also in the blood in hypertriglyceridaemia is associated with acute pancreatitis. The current study was therefore designed to further investigate osmolality and the onset of acute pancreatitis. 111 patients with clinical and biochemical pancreatitis were studied retrospectively. Their plasma osmolality was calculated using strict biochemical criteria and compared with 60 control patients with abdominal pain of non-pancreatic origin with similar age and sex distribution. 21 of the 111 patients had predicted severe attacks, of which 7 were fatal. The control patients had a mean plasma osmolality of 293 (interquartile range 286 – 297) mmol/l. This was not significantly different from the 90 patients with mild pancreatitis (mean 290 : interquartile range 281 – 299). However, the 21 patients with a severe attack had a raised plasma osmolality (mean 313 : interquartile range 293 – 333) which was significantly greater than the other patient groups (p < 0.001, Mann-Whitney U test). Since osmolality appears to be better correlated than either raised glucose or urea as an independent variable, plasma hyperosmolality may be a useful early predictor of a severe attack of pancreatitis, as well as providing possible evidence on the pathogenesis of this condition.

**W56**

**OXYGEN THERAPY IMPROVES ULTRASONIC IMAGING OF THE PANCREAS.**

**Marshall R.E.K., Steger A.C., Delicata R., Wafata J., Wyatt A.P.**

Dept. of Surgery & Radiology, Brook Hospital, Shooters Hill Road, London SE18.

Ultrasound (US) is a common investigation for upper abdominal complaints but may fail to visualise the pancreas due to the presence of bowel gas. Normobaric oxygen has been used successfully to treat the gas filled cysts of pseudocystic coil. On this basis oxygen has been given prior to ultrasound scanning to improve pancreatic visualization.

38 consecutive patients with upper abdominal complaints requiring US investigation were randomised to 2 groups: Group1: Control - no oxygen, (n=30, 14 male, 16 female, mean age 61.9 ± 17.8 years.); Group 2, (n=28, 14 male, 14 female, mean age 61.4 ± 14.5 years.) received oxygen therapy (100% humidified at 10l/min. for 8-10 hours prior to the US). The radiologist was unaware of the randomisation. Pancreatic visualisation was graded good, moderate or poor.

Mean PaO2 in group1 was 10.9 ±1kPa and in group 2 was 36 ±10.5kPa (p<0.001 unpaired t test). Pancreatic visualisation was: Good - group1: 6, group 2: 19 (Chi2 = 8.29, p< 0.01), Moderate - group1: 8, group 2: 4; Poor - group1: 14, group 2: 5 (Chi2 = 4.23, p< 0.05). Normobaric oxygen raised arterial PaO2 and was associated with improved pancreatic visualization.

Oxygen therapy is a safe, cheap non-invasive method of improving pancreatic ultrasonographic visualisation and may act by reducing overlying bowel gas.

Dynamic contrast-enhanced computed tomography (C.T.) is currently the preferred imaging technique in patients with severe acute pancreatitis suspected of developing a pancreatic collection. However, large doses of iodinated contrast are required, amid official concern about accumulated irradiation from C.T. Developments in magnetic resonance (M.R.) imaging, such as “turbo” fast spin-echo (F.L.A.S.H.) sequences, improved resolution and the availability of gadopentetate dimeglumine contrast enabled us to develop a technique analogous to dynamic C.T. The aim of the study was to compare both techniques for the detection of pancreatic necrosis and other complications. Thirty-two patients (18±14; median age 55 years; gallstones=19; alcohol=5) with severe acute pancreatitis (Atlanta criteria) were scanned using axial T2-weighted spin-echo and axial-coronal gradient-echo turbo-F.L.A.S.H. M.R. sequences (Siemens Magnetom, 1.0T), acquiring 11-15 slices (5mm) in one breathhold (18s), and in demonstrating gallstones (C.T.: 10/19; M.R.: 19/19). Dynamic M.R. imaging should be regarded as a front-line imaging technique in severe acute pancreatitis, and offers advantages over C.T. in terms of no radiation risk, low-volume non-toxic contrast, and better characterisation of fluid collections.


Surgery W58-W63

PROSPECTIVE RANDOMISED TRIAL OF LAPAROSCOPIC (LNF) VERSUS OPEN (ONF) NISSEN FUNDOPICATION D.J. Watson, R. Gourlay, J. Goble, M.W.R. Reed, A.G. Johnson & C.J. Stoddard Department of Surgical and Anaesthetic Sciences, Royal Hallamshire Hospital, Sheffield, U.K.

In order to evaluate whether laparoscopic approaches reduce the short term morbidity of anti-reflux surgery, 30 patients with confirmed gastro-oesophageal reflux have so far been entered into an ongoing prospective randomised trial of laparoscopic versus open Nissen fundoplication.

Methods: Both the laparoscopic and open procedures were standardised to an identical short, loose 360° Nissen fundoplication and a posterior repair. To exclude bias, randomisation was performed in the operating theatre and the same surgeon performed both procedures. Preliminary training in LNF was undertaken before the trial. All patients were allowed oral fluids on the first post-operative day, soft food on the second and were allowed home after 3 days if possible, irrespective of the surgical technique.

Results: All figures are median (range). 16 males and 14 females, age 47 years (26 - 71) were randomised (14 ONF & 16 LNF). Operating time was 72 minutes (47 - 154) for LNF versus 37 (23 - 52) for ONF. 2/16 LNF were converted to open procedures. Post-operative hospital stay was 3 days (4 - 4) for LNF and 4 (3 - 18) for ONF. Four patients developed complications, all following ONF (severe duodenal ulcer - 1, respiratory infection - 1, urinary retention - 2). All patients were free of reflux symptoms at 3 months, confirmed by 24 hour pH testing, oesophageal manometry and gastroscopy. One patient after ONF reported dysphagia at 3 months. This was the only patient not to describe a good or excellent outcome 3 months after surgery.

Median time to return to normal activity was 2 weeks (1 - 6) following LNF and 8 weeks (3 - 12) following ONF.

Conclusion: These preliminary results suggest that laparoscopic fundoplication takes longer and results in a less open Nissen fundoplication, but results in earlier hospital discharge and more rapid recovery. At 3 months symptom relief is identical.

CRTHERAPY WITH LIVER RESECTION FOR THE TREATMENT OF LIVER TUMOURS McCall J.L., Ross W.B., & Morris D.L. University Department of Surgery, The St George Hospital, Kogarah, New South Wales, Australia

Following liver resection for cancer a resection margin of less than lcm is associated with a 50% risk of local recurrence at one year. The risk approaches 100% when the margin is histologically involved. We have used cryotherapy for unresectable tumours with encouraging results. This paper reports the early results of combining hepatic cryotherapy with liver resection in patients resected with an inadequate margin, or with contralateral residual disease.

20 patients underwent major (15) or segmental (5) liver resection, of whom 17 had colorectal metastases. The Cryotec liquid nitrogen system was used to freeze the resection margin using a plate probe in 14 patients while 8 patients with one to six lesions in the retained liver of 9 patients were treated with an insulated cylindrical probe under ultrasound control, at the time of resection. One procedure was non-curative. The resection margin was histologically involved in 13 patients and the remainder had less than lcm clearance. There was no 30 day mortality but 20 major complications occurred in 11 patients, including 7 bile leaks and 1 benign hepatic duct stucture. All patients have been followed up clinically and by serial CEA and CT scan. At a median 10 (range 1-30) months follow-up 6 patients have developed liver recurrence of whom 3 also had distant recurrence. 5 of the liver recurrences are multifocal and one has recurred at the resection margin; 1 patient who had cryoablation to the resection margin only, 2 patients developed liver recurrence at 3 and 5 months follow-up. 14 patients are alive with no evidence of recurrence and non CEA.

Cryoablation can be used to extend the limits of resectability but is associated with a high incidence of bile leak. While not a substitute for adequate resection, the early local recurrence rates on patients with inadequate resection margins are encouraging.

ADVANCED DIFFUSE PERITONITIS MANAGED BY PLANNED MULTIPLE LAPAROTOMIES UTILISING ZIPPERS / VELCRO ANALOGUE FOR TEMPORARY ABDOMINAL CLOSURE - A PROSPECTIVE STUDY Dev complex Parikh, Professor Am, Parikh, Navan Shah, H Shah (introduced by Professor Sir R Shields) Jagmohan Hospital, Navrangpura, Ahmedabad - 380 009 India

Temporary Abdominal Closure (TAC) is defined as a series of planned multiple operative procedures performed at 24 hours interval with a commitment to reexplore patient's abdomen following initial corrective operation. This is a prospective study of 58 patients treated by TAC for severe suppurative peritonitis. TAC was performed in 6% of all patients with peritonitis having fulfilled one of the following criteria: (i) peritonitis of more than 48 hours duration; (ii) faecal peritonitis of more than 24 hours duration; (iii) inability to eliminate source of infection at the initial operation; (iv) patient's condition too poor to undergo curative procedure (APACHE II score >10).

A total of 967 laparotomies were performed and the abdomen closed temporarily in 58 patients utilising a zipper (n=34) and Velcro analogue (n=24). An average of 8.2 procedures were necessary to control the infection. In 42% of the patients additional surgical complications were recognised and repaired after the initial operation. 15 Patients were artificially ventilated for an average of 3.4 days. The median duration of therapy was 19 (range 10-102) days. The average number of days between days 2 and 9 (median,11) after initiation of therapy in 86% uncomplicated wound healing was observed after definitive wound closure. In the treated group APACHE II score predicted mortality of 64% The actual mortality was 20.6% .

Conclusion: The mortality of advanced diffuse peritonitis was reduced from a predicted 64% (range 26-94%) - predicted by APACHE II) to 20.6% with the technique of planned multiple laparotomies utilising Zipper / Velcro analogue for temporary abdominal closure.
SUB-TOTAL COLECTOMY OR SEGMENTAL RESECTION FOR MALIGNANT LEFT-SIDED COLORECTAL OBSTRUCTION: A RANDOMISED CLINICAL TRIAL
Z.H. Krzowski, A. Bruno and S.J. Ross on behalf of the SCOTIA Study Group (introduced by P.W. Brunt), Department of Surgery and Health Services Research Unit, University of Aberdeen

One hundred patients from 12 centres presenting with presumed malignant left sided colorectal obstruction were randomised into a prospective comparative trial. Ten patients were withdrawn after randomisation leaving 46 patients randomised to subtotal colectomy (STC) and 44 to segmental colectomy following on-table irrigation (SCI). The groups were well matched for age, sex, risk (APACHE-II score), site and stage of tumour. Data were analysed on an 'intention to treat' basis.

Duration of operation was similar (STC: 130 min IQR 95-159; SCI 140 min, IQR 118-180). The differences in morbidity and mortality between the two groups did not reach statistical significance.

<table>
<thead>
<tr>
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<th>STC n = 46</th>
<th>SCI n = 44</th>
</tr>
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<tbody>
<tr>
<td>Death</td>
<td>6 (13%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Wound sepsis</td>
<td>2 (5%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Intrapерitoneal sepsis</td>
<td>4 (9%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>4 (9%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Postoperative stay</td>
<td>12 days</td>
<td>11 days</td>
</tr>
</tbody>
</table>

At the first hospital review, daily bowel frequency was significantly greater for the STC group (median 2, range 1-5) than the SCI group (median 1, range 1-3) (M-W p = 0.008). This result was confirmed by patient questionnaire at 4 months post-operatively and more patients in the STC group (14/34) had consulted GP for bowel problems than the SCI group (3/33) (X² =13.8; p = 0.02). This study shows no significant difference in outcome between the two groups except in bowel frequency which was not perceived as a problem by patients.

CIMETIDINE PREVENTS POSTOPERATIVE SUPPRESSION OF IMMUNE FUNCTION FOLLOWING COLORECTAL CANCER SURGERY
Adam W., King D., Lubowski D., Morris D.I.
University Department of Surgery, The St George Hospital, Kogarah, N.S.W. 2219, Australia

AIM: To determine if perioperative treatment with cimetidine could prevent the immunosuppression that follows colorectal surgery.

METHODS: Fifty consecutive patients undergoing elective colorectal resection for cancer were enrolled in the study. Five were excluded. Patients were randomly assigned to treatment and control groups. Treated patients received cimetidine for five days orally at a dose of 400mg bd, then intravenously from the time of operation at a dose of 200mg 6 hourly for 12 doses. A control function was measured before and 48 hours after surgery by skin antigen testing for delayed hypersensitivity reactions, measured as the area of induration (Multitest Pasteur) and by in vitro tests of lymphocyte proliferative ability and flow cytometric measurement of lymphocyte subset numbers. Age, stage of disease and blood transfusion rate was very similar in the 2 groups.

RESULTS: Following surgery there was a significant fall in all lymphocyte subsets in control patients, as well as a 52% drop in mean lymphocyte proliferation and 71% drop in mean skin reaction area. In cimetidine patients there was no significant fall in lymphocyte proliferation or in skin hypersensitivity reactions in the cimetidine group. There was a significant fall in total circulating lymphocytes but 8 cell numbers were preserved.

CONCLUSION: Treatment with cimetidine reduces the degree of Immunosuppression that follows colorectal resection. Preservation of perioperative immune function has potential to reduce septic complications, and possibly improve cancer survival.

LONGTERM OUTCOME OF MEDICAL MANAGEMENT OF GASTRIC ULCER (GU). GS Murali, KD Barhman, C Rosaton, J Beresford.
Rotherham General Hospital W3 and 'SmithKline Beecham Pharmaceuticals, Welwyn Garden City, UK.

INTRODUCTION We examined the longterm (up to 15 years) outcome of maintenance therapy (MT) in GU, about which there is little data. PATIENTS & TREATMENT Between 1976-91, 1290 GU patients were seen of whom 536 had GU alone (no duodenal or oesophageal disease). Of these, 376 were treated exclusively by medical means (MT) and 124 by surgery (Surgery). Medical treatment was with H2RA mainly standard low dose, CIM 0.4g, some with ranitidine (RAN) 0.15g or, those with severe disease, at full dose (CIM ≥1g, RAN ≥3g). Endoscopy was done yearly or whenever symptoms recurred. Follow up was 7mo-15.5yrs (mean 5.7yrs). RESULTS Healing occurred within 3 months in 338/376(90%) patients; in 38% (10%) it took longer (ie refractory [REF] disease) and some needed high doses of H2RA. Longterm outcome: Ulcer: recurrence rates (Complications)

- No therapy 24/51 (47%) 2/70(3%) No MT
- Low dose MT 50/170(29%) 7/150(5%) MT
- Full dose MT 13/136(10%) 4/150(3%) Mt

"No VisMDI p=0.003 #leed 10; omission 5; perforation 2 REF vs non-REF GU: Relaxation on MT (low dose 5/13(39) vs 4/45 (17%); full dose 5/19(26%) vs 8/117(7%)[p=0.01]. Surgery 12/34(3%) were operated for: recurrence:refractoriness 4, perforation 2; obstruction 1; malignancy 3 (1 proved benign); pain despite healing 1; doctor's choice 1. One drug post-operatively. Malignancy on MT developed in 2/376(0.5%) Side effects Only 10 had MT stopped for suspected side effects.

CONCLUSION Without MT, almost half of GU patients relapse. MT markedly reduces relapse rates, the higher dose more so than the lower dose; this benefit lasts over many years. Treatment is safe. REF GU has a moderately high relapse rate, even full dose MT. Complications are uncommon and malignancy rare.
BLEEDING GASTRIC ULCER (GU) IN THE H2RA ERA. CS Railu, KD Bardhan, C Royston, J Beresford. Rotherham General Hospitals NHS Trust & SmithKline Beecham Pharmaceuticals, Wath upon Dearne, UK.

INTRODUCTION Little is known about the long-term outcome of GU patients presenting with bleeding in the H2RA era.

PATIENTS Between 1976-91, 1280 pts were seen of whom 536 had GU alone, in 51 patients there is no duodenal or oesophageal disease, of whom 178 (33%) presented with bleeding. DEMOGRAPHY: Bleeding v nonbleeding (n=358): GU: age <60, 69±52%; pain at presentation, 50±85%; history: C63±40%; history: smoking, 45±16%; NSAID use, 43±20%; large GU, 34±19% (all p<0.001).

IMMEDIATE OUTCOME 19 (10.5%) had early surgery but in another (2.1%), severe multisystem disease precluded operation and they died. The remaining 157 pts were managed medically. EARLY OUTCOME Healing occurred in 130 pts in <3 months, mainly on cimetidine (CIM) Ig daily; 11 pts took longer. Symptomatic Two in 1/100 patients responded to refractoriness. Deaths 9 died from unrelated causes. Others two defaulted and 3 were still on healing therapy.

LATE OUTCOME After healing, 23 pts had no further therapy. 118 had prophylactic maintenance therapy (MT), 116 with H2RA (and with misoprostol). The elderly and those with severe disease had 1.2±0.3g. ranitidine (RAN) >0.3g. The other half had standard low dose MT, mainly CIM 0.4g and occasionally RAN 0.15g. Endoscopy was done yearly or whenever symptoms recurred. These 141 pts were followed up for a mean of 3.2 years (range 0.2-14).

Crude relapse rate Relapsed
No MT 11/23 (48%) 2
After MT stopped 2/7 (29%) 1
Low dose MT 5/8 (62%) 2
Full dose MT 4/5 (80%) 0
Misoprostol MT 2/5 (40%) 0
(* All managed conservatively)

CONCLUSION Patients with bleeding gastric ulcer tend to be older, have pain less often at presentation, have a short history, large ulcer and use NSAID more frequently. About 10% need immediate operation to control hemorrhage. In the vast majority bleeding stops spontaneously. Their subsequent medical management with H2RA is satisfactory: healing occurs rapidly in most. Maintenance therapy sustains remission and rebleeding is uncommon.

PUBLIC EDUCATION ABOUT DYSPESIA AND GASTRIC CANCER: A PILOT STUDY Peter McCulloch & David Melling (Introduced by CR Mackie) Department of Surgery, University of Liverpool, and Aintree Hospital Trust.

Stomach cancer carries a poor prognosis in Britain, partly because mild and non-specific early symptoms lead to delayed diagnosis. In an attempt to increase early diagnosis, we have sent letters to all patients over 40 in a population of 45,000, urging patients with undiagnosed recent-onset dyspepsia, weight loss, anorexia or vomiting to attend promptly for investigation: responders underwent urgent gastroscopy, plus other investigations if indicated. This provided an opportunity to assess the prevalence and causes of dyspepsia in the over 40s in the community. The effectiveness and comprehensibility of the letter was presented on non-dyspeptic surgical outpatients over 40 years old. 15,698 letters were sent out, of whom 137 patients (0.87%) presented for endoscopy. 370 letters (2.36%) were returned and there were three complaints. 33/37 (88%) outpatients would have responded positively to the letter if symptomatic. The diagnostic yield is shown below (Table).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
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<tbody>
<tr>
<td>Gastritis</td>
<td>21 (15.4%)</td>
<td>26 (19.2%)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>23 (16.82)</td>
<td>28 (21.62)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1 (0.72%)</td>
<td>2 (1.52%)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>2 (1.52%)</td>
<td>4 (3.20%)</td>
</tr>
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<td>Gastritis</td>
<td>21 (15.4%)</td>
<td>26 (19.2%)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>23 (16.82)</td>
<td>28 (21.62)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1 (0.72%)</td>
<td>2 (1.52%)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>2 (1.52%)</td>
<td>4 (3.20%)</td>
</tr>
</tbody>
</table>

A significant treatable cause was found in 55 (63/115) patients. One malignancy was found per 34 gastroscopies (2.2%). No decrease in rate was noted in non-referrals for gastroscopy. This intervention appears effective in bringing to light undiagnosed gastrointestinal disease. Community studies are indicated to evaluate its usefulness.

H. pylori ERADICATION IN THE AFRICAN SETTING: RE-INFECTION AND DUODENAL ULCER RECURRENTNESS. JA Low, W. Lucke, K. Jaskiewicz, A L Astovovic, TA Winter, and IN Marks. Gastrointestinal Clinic and Departments of Medicine, Anatomical Pathology, and Microbiology, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa.

The protective effect of H. pylori (HP) eradication on DU relapse risks for as long patients remain uninfected. Re-infection rates are low in developed countries, where HP prevalence is low. Re-infection following eradication has not been well studied in populations with high HP carriage rate. AIM: To determine the effect of HP eradication on the natural history of DU disease, and to determine the incidence of re-infection in our high prevalence population.

METHODS: 45 HP positive patients with DU disease were treated with 7 (n = 17) or 14 days (n = 31) of "Triple Therapy" (TT). Endoscopy was performed at entry, following ulcer healing therapy, 4 weeks after cessation of TT and 6 and 12 months later, or whenever patients suffered recurrent dyspeptic symptoms. Antral HP status was determined at each endoscopy by RUT, histology (Giemsa method) and culture of biopsies taken within 5 cm of the pylorus.

RESULTS:

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>ERADICATED</th>
<th>NON-ERADICATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>Smokers</td>
<td>22 (81%)</td>
<td>17 (94%)</td>
</tr>
<tr>
<td>Re-infected</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

H. PYLORI DOES NOT INCREASE THE INCIDENCE OF DYSPESIA ASSOCIATED WITH NSAID GASTROPATHY. MM Arnold, F. McKenna, BNA Hamid (Introduced by WDW Rees) Trafford General Hospital, Manchester.

It has been reported that HP in patients with NSAID-gastropathy increases the incidence of dyspepsia (ref). We have examined antral biopsies from 110 patients taking either a continuous standard dose NSAIDs (group 1) or non-NSAID analgesics (group 2) in whom gastroduodenal lesions were scored according to a modified Lanza scale. 67 patients had rheumatoid arthritis, 45 of whom were taking NSAIDs and 27 of the remainder were taking NSAIDs mostly for osteoarthritis. HP organisms were found in 39% of patients in group 1 and 42% of those in group 2. There was a lower colonisation rate in patients on DMDAARDs but this was not significant. Smoking and alcohol were not related to the presence of lesions or to HP status.

There was a highly significant association between NSAID use and Lanza grade (p<0.001,χ2) but no association between HP status and Lanza score (p=0.17,χ2). In patients on NSAIDs, lesions were often asymptomatic and there was no association between the presence of HP and dyspepsia (p=0.66,χ2).

We conclude that HP does not increase the incidence of dyspepsia in patients with NSAID Gastropathy and that HP plays only a minimal role in the development of NSAID associated peptic ulceration.

<table>
<thead>
<tr>
<th>Lanza grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 HP+</td>
<td>1 (0)</td>
<td>3 (1)</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>HP-</td>
<td>7 (4)</td>
<td>2 (1)</td>
<td>12 (8)</td>
<td>4 (2)</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Group 2 HP+</td>
<td>8 (1)</td>
<td>4 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>HP-</td>
<td>16 (0)</td>
<td>2 (2)</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

The number of patients with symptoms are in ()

STUDIES OF GASTRIC EMPTYING AND HISTOLOGY BEFORE AND AFTER THE ERADICATION OF HELICOBACTER PYLORI IN ENDOSCOPY-NEGATIVE DYSPEPSIA

S18

Methods: Nineteen dyspeptic patients were studied before and after treatment: upper GI endoscopy, antral and fundic biopsies for urease test and histology, semi-solid meal gastric emptying (T1/2) for whole stomach, antrum and fundus) labelled with 10–12 MBq of 111In. Histological gastritis was assessed blindly using a system based on the severity of the inflammatory cell infiltrate. Results: HP was eradicated in 17 patients in whom mean whole stomach T1/2 decreased from 45 min (SD 15) to 30 min (SD 14) (P<0.05, paired T-test). Antral and fundic T1/2 were unchanged. In the two patients in whom HP eradication failed, whole stomach T1/2 increased. Histology showed a predominantly antral gastritis that improved, but was not abolished by HP eradication.

Conclusion: In man, HP seems to have a modest gastroparetic effect, not localized anatomically to the antrum which is the site of maximal mucosal inflammation, but is diffuse, affecting the whole stomach.

H. PYLORI LOWERS DUODENAL BUT NOT CORPUS SOMATOSTATIN mRNA, IN DU PAtIENTS. N.Toker, SF. Moss, S Legon, J Calam, Royal Postgraduate Medical School, UK

Somatostatin is the main inhibitory peptide of the gut. H. pylori suppresses antral expression of somatostatin, and this may explain the increased gastrin release. Somatostatin normally inhibits parietal cells, and H. pylori increases acid secretion in duodenal ulcer (DU) patients. Therefore we examined the effect of H. pylori eradication on somatostatin expression in the gastric corpus mucosa of DU patients. Somatostatin also regulates mucosal function in the duodenum which is the site of ulceration, so we also studied the duodenal mucosa. Local somatostatin release cannot be measured directly, so we analysed somatostatin mRNA which reflects the rate of peptide synthesis.

Somatostatin mRNA was measured by Northern blotting of extracts of 5 biopsies per region, as described previously. Corpus biopsies were taken from the middle of the greater curve and duodenal bulb biopsies were taken away from sites of ulceration or obvious inflammation. Eight infected patients with active DU were studied before and 4–8 weeks after the end of successful eradication therapy, which also healed their ulcers.

We previously showed a significant 1.9 x rise in the median somatostatin mRNA/RNA ratio the gastric antrum after eradication therapy. The median ratio rose similarly by 2.1 x in the duodenal bulb after eradication of H. pylori. In marked contrast, eradication of H. pylori had no significant effect on the somatostatin mRNA/RNA ratio in the gastric corpus.

The lack of effect of H. pylori on corpus somatostatin is consistent with sparing of this region, and the normal responsiveness of parietal cells to gastrin in DU patients. Less inhibition of physiological or inflammatory processes in the duodenum by somatostatin might contribute to ulcer formation.
Liver T74-T81

SEROYTIC VARIATION AND CLINICAL CHARACTERISTICS OF CHRONIC HEPATITIS C DETECTED AT BLOOD DONOR SCREENING.

GLA Bird, E Spence, RN M MacSween*, D Frame*, P Yap*, P Simmons*, FR Mills, Departments of Gastroenterology and Pathology, Western Infirmary, Glasgow, Scottish National Blood Transfusion Service* and Department of Medical Microbiology*, University of Edinburgh, UK.

In the first two years of screening for HCV (1991-1993), the Glasgow and West of Scotland Blood Transfusion Service has tested 305,012 volunteer blood donations, of which 214 have been positive for HCV, as determined by 2nd generation ELSA, RIBA-2 testing and PCR. We have evaluated the clinical findings, histological severity of disease and their relationship with HCV serotype in asymptomatic donors with chronic HCV.

54 asymptomatic subjects (mean age 32, range 22-46, 22 females) underwent clinical evaluation, liver biopsy and typing by restriction fragment length polymorphisms. In 5 there was a history of jaundice or hepatitis. 22 subjects had abused IV drugs (IVDA). 16 patients had received blood products and one drug abuser also had a blood transfusion. After exclusion of subjects with tattoos and/or pierced ears, occupational risk factors and homosexuality, only 2 had no identifiable risk factors. In the 39 with a clearly defined risk factor (transfusion and IVDA), the mean interval between HCV exposure and liver biopsy was 12 years (range 4-30). All subjects had evidence of chronic liver disease as shown by raised serum aminotransferases (mean AST 68, range 19-220, normal range 5-30), ALT 132, range 49-1035 (normal <80) and/or clinical signs (n=18). The liver biopsy was abnormal in all subjects with features of a very low grade chronic hepatitis comprising portal inflammation and periporal features now recognised as characteristic of chronic HCV infection; one subject had an established cirrhosis. Serotyping (n=35) showed no relationship to mode of transmission, biochemical or histological severity of disease (17 type 1, 4 type 2, 14 type 3).

These findings confirm that chronic hepatitis C is present in all asymptomatic subjects with HCV viremia irrespective of clinical features and mode of transmission are not related to HCV serotype.

T75

HEPATOCELLULAR CARCINOMA (HCC) IN AUTO-IMMUNE CHRONIC ACTIVE HEPATITIS (AIH): THE ROLE OF HEPATITIS C (HCV) INFECTION.

SD Ryder, J Koskinas, IQ McFarlane, PM Rizzi, N Naoumov and R Williams. Institute of Liver Studies, King’s College Hospital, London.

Background. The risk of hepatocellular carcinoma in AIH is thought low, despite the presence of long standing cirrhosis. With the increasing recognition of HCV infection in AIH and cryptogenic liver disease we examined 8 cases of HCC complicating AIH. Patients. All 8 patients presented with HCC between 1980 and 1992, 4 male, 4 female. All patients had steroid responsive AIH with positive anti-smooth muscle and ANF. Median duration of disease was 24.6 years and all patients had biopsy proven cirrhosis. 4 patients had a history of blood transfusion and 1 previous intravenous drug abuse. One patient had post transfusion hepatitis 7 years prior to presentation with HCC. One patient had HCC diagnosed incidentally, at transplantation and is still alive 3 years post-transplant. The other 7 presented with advanced symptomatic disease, median survival 4.5 months.

Methods. Serum samples (up to 9 years pre HCC diagnosis) were tested for antibodies to HCV (Abbott RIBA) and Polymerase chain reaction (PCR) for HCV. Liver tissue from liver adjacent to HCC was subjected to PCR using primers from the 5' non-coding region as were samples from prior liver biopsy specimens in all patients (up to 19 years prior to HCC). Results. At presentation with HCC 6/8 patients had evidence of HCV infection. 2 patients had positive antibodies to HCV. These patients and 2 others had HCV RNA detectable in serum. Two additional patients with negative serum PCR had HCV RNA detected in liver tissue. Retrospective testing showed only one patient had HCV RNA in liver at presentation with AIH and probable acquisition of HCV infection from transfusion in 4 patients. Median time from HCV infection to HCC was 5 years. Conclusions. HCC complicating AIH is frequently associated with unsuspected HCV infection but this was usually contracted after diagnosis of autoimmune liver disease. PCR in liver tissue is required to make the diagnosis of HCV infection in these immunosuppressed patients. HCC supervenes rapidly following HCV infection in these, already cirrhotic, patients.

T76

TIMP-1 ACTIVITY IN LIPOCYTE CONDITIONED MEDIA PREDOMINATES OVER COLLAGENASE EVEN AFTER TNFa STIMULATION

Iordache IE, Goddard S, Murphy G* & Arthur MP, University Medicine, Southampton General Hospital, UK. *Strangeways Research Laboratory, Cambridge, UK.

We have recently described expression of the collagenase inhibitor Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) by activated hepatic lipocytes and demonstrated that TIMP-1 mRNA expression is enhanced in comparison with interstitial collagenase (IC) mRNA in cirrhotic liver. These studies describe investigation of the I/CTIMP-1 activity relationship in a cell culture model of lipocyte activation.

Human hepatic lipocytes were extracted from normal donor liver, and the margin of hepatic resection as previously described and cultured on plastic for 21-44 days. In addition passaged lipocytes (6th passage) from two isolations were established in culture on plastic.

By Northern analysis, mRNA for IC could not be detected in total lipocyte RNA, but was present after stimulation with TNFa 30ng/ml. In contrast TIMP-1 mRNA was present in unstimulated lipocytes and up-regulated in response to TNFa.

By activity assay of serum free conditioned media, IC could not be detected in both unstimulated and TNFa stimulated primary lipocyte cultures (n=4) and passaged lipocytes (n=6). In contrast TIMP-1 activity was present in unstimulated primary and passaged cultures 2.5 (1.6, 2.6, n=4) and 9.28 (2.9, n=6) mean (± SD) units/106 cells/24 hrs respectively. Furthermore, TIMP-1 activity in paired cultures was up-regulated in response to TNFa: 3.69 (2.6, n=4) and 11.42 (± 5, n=6) mean (± SD) units/106 cells/24 hrs respectively.

In this model of lipocyte activation, TIMP-1 activity remains predominant even in the presence of up-regulated IC transcription. Predominance of TIMP-1 expression may favour the accumulation of interstitial collagens in liver fibrosis.