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**T201**

**HLA-C LOCUS GENES AND SUSCEPTIBILITY TO AUTOIMMUNE HEPATITIS (AIH).** M.D.J. Streatfield, Lj Thomson, P.T. Donaldson and Roger Williams. Institute of Liver Studies, King’s College Hospital, London, UK.

Previous studies of Caucasoid patients with AIH at this Institute have identified associations with the DRB1*1001 (DR3), DRB3*0101 (DR4-x) and DRB4*0101 (DR4) class II HLA alleles. The class I HLA-C locus is of interest as it maps telomeric to the DRB locus, lying in between the A and B loci-and has a potential role in regulating natural killer cell function. To date only one study (Lepage et al. Tissue Antigens 1985;1:190-197) has examined the role of the HLA-Cw serologically defined HLA-Cw specificities in AIH. Despite population heterogeneity, small numbers and the serological methods used, their analysis suggested an association between AIH and HLA-Cw7. AIM: To re-examine this hypothesis we have performed PCR-SSP genotyping of the HLA-C genes in a group of 62 adult Caucasian patients with type 1 AIH and 50 racially matched controls. Technical advice and primers were kindly supplied by M. Bunce et al., Oxford, UK. RESULTS: The association was strongest in those patients possessing the HLA-Cw*0701 allele (53% of patients cf. 30% of controls, p < 0.025). The other Cw07 alleles, *0702, *0703 and *0704 which encode the same serological specificity, Cw7, were not associated. The Cw*0401 allele was found at a reduced frequency suggesting a protective effect (6% of patients cf. 24% of controls, but was not significant when corrected for multiple testing). There were no other significant associations.

**Discussion:** This is the first study to use molecular genotyping techniques to examine the HLA-C locus in AIH. This methodology detects a number of newly identified Cw alleles which are not recognised by serology. Linkage studies suggest that the gene encoding Cw7 forms part of the A-B-DRB3*0101-DRB1*0301 extended haplotype. Thus our finding of an association between HLA-Cw7 and AIH may simply reflect linkage disequilibrium with the susceptibility haplotype. The HLA-Cw*0701 association was weaker than that observed in our previous studies for the DRB locus. This is further evidence that the primary susceptibility site lies within the class II rather than the class I region. It is also possible however, that HLA-Cw7 may contribute to this disease by virtue of its interaction with natural killer cells.

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**T202**

**HUMAN HEPATIC SINUSOIDAL ENDOTHELIAL CELLS UPREGULATE ADHESION MOLECULE EXPRESSION AND CHEMOKINE SECRETION IN RESPONSE TO PROINFLAMMATORY CYTOKINES IN VITRO.** G. McNab, SC Afferd, C. Merland, AJ Stuart, K. Joplin and DH Adams. The Liver Unit, Queen Elizabeth Hospital, Birmingham.

Sinusoidal endothelium plays a vital role in regulating the recruitment of leukocytes to the liver during physiological immune surveillance and pathological inflammation. Leucocyte recruitment depends upon adhesion to endothelium and subsequent migration into tissue. The expression of endothelial adhesion molecules and secretion of chemoattractant chemokines (that can trigger leukocyte adhesion and migration) provide important regulatory steps in this process. In order to investigate the role of SECs in leucocyte recruitment to the liver we have developed techniques for the isolation and long-term culture of human SECs and used them to study the regulation of adhesion molecule expression and chemokine secretion.

Endothelial cells were isolated from human liver by a 3-step process involving (i) collagenase perfusion (ii) density gradient centrifugation and centrifugal elutriation (iii) immunomagnetic purification using mAb to CD31 and vascular adhesion protein-1 (which is selectively expressed on hepatic endothelium in vivo). SEC proliferated in response to vascular endothelial growth factor (VEGF) allowing us to establish long-term SEC cultures that had a characteristic endothelial morphology with fenestrae and sieve plate on electron microscopy. SECs maintained a characteristic phenotype in culture (CD31+, CD34+, VAP-1 and NG-2+) that was distinct from dermal and microvascular endothelial cells (CD31+, CD34+, VAP-1-). Treatment of SECs with TNFalpha, IL-1 or IFNgamma induced upregulation of the adhesion molecules ICAM-1 and VCAM-1 and the costimulatory molecule CD80. Treatment of SECs with IL-1 or IFNgamma induced expression and secretion of the chemokines IL-8 and MCP-1. TNFalpha and TNFbeta had no effect on chemokine secretion.

**Conclusions:**
1. The use of VEGF permits the long-term culture of human hepatic SECs that maintain the characteristic phenotype in culture.
2. Treatment of cultured SECs with proinflammatory cytokines induces the expression and secretion of adhesion molecules and chemokines that are vital for leukocyte transendothelial migration.

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**T203**

**IL-18, TNF-alpha, TGF-beta AND c-myc GENE EXPRESSION IN HUMAN HEPATOCELLULAR CARCINOMA (HCC).** M. Bortolami, C. Venturi, C. Carlato, R. Scalaletta, R. Pucciarelli, M. R. Chiarandone, R. F. Riva, R. Naccarato (introduced by M. Chiarandone).

Gastroenterology of II Dept. Surgery, Padua University, Italy.

Studying oncogenes, growth factors and cytokines from the same tumor specimen may help in understanding their role in cancer biology and their reciprocal relationships. Aim of the study was to investigate the gene expression of proinflammatory cytokines (IL-18 and TNF-alpha), growth factors (TGF-beta) and oncogenes (c-myc) in HCC by means of a quantitative comparative non-radioisotopic RT-PCR technique. Method: specimens of both tumor (T) and peritumoral tissue (PTT) were obtained from 14 patients with HCC (MF: 10.4; age 23-76 yrs; surgical resection). 10/14 tumors were in cirrhosis and 4 in normal liver. As a control group we used 5 pre-implant graft livers (NL). Total RNA extracted from tissues was reverse transcribed into cDNA and amplified by PCR using primers specific for IL-18, TNF-alpha, TGF-beta and c-myc (Clontech). PCR products were resolved on polyacrylamide gel, silver-stained and quantified by densitometric scanning. The following table shows the results (means±S.D.) in cirrhocites with HCC expressed as a ratio over the control beta-actin; no specific changes being observed in HCC without cirrhosis.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IL-18</th>
<th>TNF-alpha</th>
<th>TGF-beta</th>
<th>c-myc</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL (6)</td>
<td>2.22±0.80</td>
<td>0.21±0.11</td>
<td>0.24±0.28</td>
<td>0.14±0.10</td>
</tr>
<tr>
<td>PTT (10)</td>
<td>2.12±1.42</td>
<td>0.59±0.34</td>
<td>0.53±0.37</td>
<td>0.56±0.24</td>
</tr>
<tr>
<td>TT (10)</td>
<td>1.20±0.56</td>
<td>0.55±0.42</td>
<td>0.24±0.37</td>
<td>0.38±0.24</td>
</tr>
</tbody>
</table>

**Endoscopy F204–F209**

**DEVELOPING UPPER GI TRACT NURSE ENDOSCOPY**

Hagan P M, Nightingale J M D, Smith E M, BatSTONE B I

There is an increasing demand for diagnostic and therapeutic upper gastrointestinal endoscopy which most units have difficulty fulfilling. While clinical assistants are used in some units they are not generally available. With recognition of the increasing development of nurse specialisation and the introduction of a Queen’s nursing role supporting nurse endoscopy at the Leicester Royal Infirmary, formal nurse endoscopists were keen to undertake diagnostic endoscopy and a proposal for the role was developed.

The proposal included practical skills training, protocol development, clinical supervision and audit provision. The role was agreed by all the GI physicians and surgeons and surgeons accepting medico-legal responsibility and vicarious liability agreed by the Trust Board. Strict exclusion criteria were agreed for the nurse endoscopy patients and included age over 75, cardio-respiratory disease, GI bleeding, dysphagia, previous gastric surgery and known liver disease.

Patients were screened and a maximum of 2.5 mg Hypnovel was administered by the nurse endoscopist. Pulse oximetry monitoring takes place throughout the procedure. Nurse endoscopy lists are carried out concurrently with those of a consultant or senior registrar. A video image of the procedure is simultaneously transmitted to the second endoscopist and allows for supervision and advice throughout the procedure. All nurse endoscopies are video recorded for audit and further training purposes.

Following training the Nurse Endoscopist has performed over 400 upper GI endoscopies. There have been no adverse events and the waiting list has been reduced by at least 4 weeks. The process of developing nurse endoscopy has also provided a good framework to standardise future endoscopy training in the hospital.
COLONIC ADENOMAS IN DIVERTICULAR DISEASE - ANALYSIS OF 1724 COLONIC EXAMINATIONS. K Ragunath, V Mani, Dept Gastroenterology, Wigan & Leigh NHS Trust Hospitals, Leigh Infirmary, Ormskirk, Lernholmes

Background: An association between colonic diverticular disease and adenomatous polyp has been documented. The aim of this paper was to study such association.

Materials & Methods: Data on 1724 consecutive, elective total coloscopy performed at the GI Unit, at the above hospital were analysed. 281 patients had diverticular disease (DD) (M:F=35:247), predominantly left sided (84%). 180 patients had colonic polyps, 90 (60%) adenomatous and 90 (60%) non-adenomatous. Of the 90 adenomas 87 (74%) were benign and 23 (26%) malignant. Age range varied from 41-80 years, 60% being between 61-80 age group. Incidence of benign adenomas in patients with DD was 37%. In the patients without DD there were 302 polyps of which 216 were adenomatous (66%) of which 47 (22%) were malignant the rest 168(44%) were benign. Age range varied from 20-80 years, 60% being between 61-80 years. Symptoms included alteration of bowel habit, abdominal pain and bleeding and were similar in both groups. Colonicoscopic snaring was successful in all benign adenomas without any major complications. Statistical analysis (Chi square) revealed a significant increase of adenomatous polyps with DD (p<0.01). There was little difference between the two groups with malignant polyps except for a significant trend with age.

Conclusions: We confirm the association of benign adenomas in patients with DD. Colonoscopy is indicated regardless of symptoms in all patients with DD for diagnosis and management.

NEW ENDOSCOPIC METHOD FOR THE TREATMENT OF VARICES: MULTI-FIXING ENDOLUMPS


Endoscopic variceal ligation using bands appears safer and more effective than injection sclerotherapy for bleeding oesophageal varices but is limited by requiring an overtube for repeated placement of bands. Endoloops are detachable self-retaining snare that have been used in the treatment of varices. Fourteen patients with canine portal hypertensive vessels of 1-5mm in external diameter comparing injection sclerotherapy, band ligation and endoloop showed that injection sclerotherapy failed to stop bleeding in vessels of 1mm (n=10), and 2mm (n=10), bands were effective in arresting haemorrhage in vessels up to 2mm diameter (n=15) and endoloops achieved haemostasis in all vessels (n=6). In conclusion, endoloop snaring is a safer, faster and less traumatic technique.

Conclusions: Endoscopic banding is the treatment of varices. Multi-fixing endoloops (in which the loop is deployed to one end and loaded with a loop of banding) loading the endoloop is simply by passage along the biopsy channel 3) experimental models have shown the endoloop to be superior to elastic bands in achieving haemostasis in large vessels. Endoloops have now been used on patients, admitted with bleeding oesophageal varices (n=9). The endoloop were placed without the use of an overtube and with the patient receiving midazolam sedation. No discomfort was reported from any patient following the application of the endoloops and complete haemostasis was achieved. No evidence of further rebleed occurred and all patients were discharged from the hospital. The endoloop remained attached for up to 3 weeks but had detached by 5 weeks. Ulceration at the site of the endoloop had resolved after 5 weeks. Conclusions: endoloop arrest bleeding from larger vessels than band ligation or sclerotherapy, 2) they can be repeatedly applied without an overtube, 3) multiple ligation is possible via the biopsy channel 4) they detach spontaneously from the varix, but can remain attached for several weeks 5) they have been used effectively in human studies.

WE MAY BE MISSING A LARGE PROPORTION OF EARLY COLONIC CANCERS

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1 Centre for Digestive Diseases, Leeds, UK 2 National Cancer Centre East, Chiba, Japan

Introduction: Basil Morson proposed the adenoma-carcinoma sequence in the evolution of colonic carcinoma and estimated that between half and two thirds of all colorectal carcinomas arise from adenomatous polyps. An explanation for the origin of the remaining one third of colorectal carcinomas was put forward by the Japanese when they reported that early colonic malignancies may appear flat or depressed rather than polypoid.

Methods: 210 consecutively encountered patients attending for routine colonoscopy were screened for flat and depressed as well as polypoid malignancies. Suspicious lesions were scrutinised with the application of topical indigo carmine stain. Small polyps were treated with hot biopsy and large by snare polypectomy. Flat elevated or depressed lesions, less than 20 mm in diameter, were treated by endoscopic mucosal resection.

Results: In total, 61 adenomas were found in 53 of the 210 patients (25%) in the study. Polyoid adenomas were the most common but the flat elevated type accounted for a large proportion (70% vs 30%). The majority of adenomas contained mild or moderate dysplasia but four were severely dysplastic and may be regarded as early carcinomas. Three of the severely dysplastic lesions were 15 mm polyoid tubulovillous adenomas but the final case was a 6 mm depression of the mucosa. Three early adenocarcinomas were found of which only one appeared polyoid. The other two were flat elevations of the mucosa with a central depression. Although, only three such lesions were identified in this study, two contained early adenocarcinomas.

Conclusions: We can confirm that flat and depressed adenomas are common in British patients. The recognition that early colonic carcinoma may appear flat or depressed has important implications. The adenoma-carcinoma hypothesis only prompts colonoscopists to search for polyoid lesions when screening for malignancy. In this small series alone, we would have missed almost half (3/7) of the early colonic cancers had we not screened for flat and depressed as well as polyoid lesions.

DIAGNOSTIC LAPAROSCOPY IN CHRONIC HEPATITIS C INFECTION: A COMPARISON WITH HISTOLOGICAL DIAGNOSIS.

G Therapondos, GH Haydon, J Piris, PC Hayes. Departments of Medicine and Pathology, University of Edinburgh, Edinburgh.

Diagnostic laparoscopy, enabling visualisation of the liver, can readily be performed under local anaesthesia and intravenous sedation. In our centre, all patients with chronic hepatitis C virus (HCV) infection undergo diagnostic laparoscopy and liver biopsy to stage their disease. The aim of this study was to assess the reproducibility of laparoscopy and to compare it with histology in the diagnosis of cirrhosis, fatty change, fibrosis and inflammatory activity in patients with chronic HCV infection.

Methods: 100 consecutive patients were studied. Two laparoscopists (trainer and trainee) were shown video recordings of the laparoscopies and they graded the appearances of the liver. Histological appearances were independently. Inter- and intra-observer variability was calculated. In 46 of the patients, the liver biopsy obtained was graded by a histopathologist using the Edinburgh Scoring System to assess fatty change, inflammatory activity, fibrosis and cirrhosis. These results and the laparoscopic grading were compared independently with the diagnostic gold standard (the diagnosis elicited from all clinical, biochemical, radiological, laparoscopic and histological results).

Results: Inter-observer variability was 4%. Major intra-observer variability was 6% for the more experienced laparoscopist and 2% for the trainee. No significant difference was found between the detection rate of cirrhosis by laparoscopy and the actual rate obtained by the gold standard. Histology, however, underestimated the rate of cirrhosis (p=0.0005). There was no significant difference in the detection of fatty change and fibrosis, but laparoscopy underestimates inflammatory activity (p=0.006).

Conclusions: Diagnostic laparoscopy is the investigation of choice for the diagnosis of cirrhosis in chronic HCV infection. It is as reliable as liver biopsy in the detection of fibrosis and fatty change; liver biopsy is superior in the assessment of inflammatory activity.
A PROSPECTIVE RANDOMISED TRIAL OF SEDATION vs. NO SEDATION IN DIAGNOSTIC UPPER GASTROINTESTINAL ENDOSCOPY

N.C. Fisher MRCP, S. Bailey RN, J.A. Gibson FRCP.
Depart of Gastroenterology, Stafford General Infirmmary, Staffordshire.

Introduction: Gastroenterologists differ in their use of sedation in upper gastrointestinal endoscopy.
There have been few studies comparing sedation and no-sedation, and we sought to clarify this by a prospective, randomised controlled trial.

Methods: Out-patients referred for diagnostic endoscopy were invited to participate in our study. Only patients with a history of dysphagia were excluded. Subjects were randomised and informed in advance. All patients were given lignocaine throat spray prior to the procedure. The endoscopist recorded duration of procedure, of biopsies taken, occurrence of arrhythmias or hypoxia, and the degree of ease of the procedure on a numerical scale. Patients were given a questionnaire with numerically graded answers and asked to complete this not less than 24hrs after the procedure.

Results: 282 patients invited before 100 agreed to participate (77M, 223F). 50 patients in each arm. No biopsies was well-matched (mean 1.33 in each group), mean duration of procedure lower in no-sedated group (3min 25sec ± 4min 5sec). Procedure slightly easier in non-sedated group (1.56 ± 1.70 on scale of 1 to 5). One patient converted from no sedation to sedation.
Non-sedated group found procedure more unpleasant (2.53 ± 1.23 on scale of 1 to 5) and were slightly less willing to have procedure done in same manner in future (1.35 ± 1.09), but only 6/50 would prefer to be done with sedation next time.

Conclusions: Endoscopy faster and easier in non-sedated group. These patients find procedure more unpleasant, but do not mind procedure repeated in same way in future.

AUDIT OF SPHINCTER OF ODDI MANOMETRY AT THE ROYAL LONDON HOSPITAL. AD Millar, DF Evans, EA Stoner, A Piotrovic, CC Ainley, GI Research Science Unit, St. Bartholomew’s and Royal London School of Medicine, London.

Sphincter of Oddi dysfunction (SOD) may cause postcholecystectomy pain, right upper quadrant pain of unknown origin (RUQ), and pancreatitis. SOD is diagnosed by sphincter of Oddi (SO) manometry. The aim of this study was to assess the usefulness of SO manometry in the management of these problems.

Methods: We reviewed the results of 53 procedures in 52 patients by a single endoscopist (CA) referred from 10 centres. Data is presented in 37 procedures on which full information is currently available. For analysis, patients have been divided according to the results of SO manometry; namely hypertensive SO with or without associated tachydyssia (HT±TO) and normal (N).

Results: Shown in the table below.

<table>
<thead>
<tr>
<th>Number</th>
<th>HTO</th>
<th>TO</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>15</td>
<td>3</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Of the 13 patients with HTO, 10 have undergone endoscopic sphincterotomy (ES) with symptom resolution in 7. Two patients are awaiting ES and 1 patient with slightly raised SO pressures, who did not undergo ES, has spontaneously improved. Of the 21 with normal SO manometry, 11 have subsequently been given alternative diagnoses, 2 of whom have died and 2 of the remaining 10 have spontaneously improved. There were no episodes of pancreatitis in the 52 patients that underwent SO manometry in this series.

Conclusions: SO manometry is a useful investigation for postcholecystectomy pain. RUQ pain of unknown origin and idiopathic pancreatitis and identifies those patients with HTO in whom ES is likely to be of benefit.

EARLY GALLBLADDER EMPTYING IS MEDIATED BY CHOLECYSTOKININ.

Gastrointestinal Unit, Western General Hospital, Edinburgh, Scotland and *Department of Medicine, Queen’s University of Belfast, Northern Ireland.

Gallbladder emptying (GE) occurs in response to cholecystokinin (CCK), released as fat and protein enter the small bowel. However, GE often occurs within 10 minutes of eating, before gastric emptying can possibly have occurred. This study investigates mechanisms of early GE.

GE was measured ultrasonically in 8 healthy male volunteers (median age 35 years) on three separate occasions in random order: 1) after ingestion of two eggs on one occasion, 2) after sham feeding to examine a cephalic phase, 3) after gastric distension to 500ml using effervescent powder. Blood samples were taken for CCK radioimmunoassay.

Mean fasting gallbladder volumes were similar on each study day. Mean fasting CCK was 6.3±0.6(SE) ng/L. The fatty meal was followed by immediate GE at a rate of 0.57ml/mint, with ejection fraction (EF) of 25% by 10 minutes. This was associated with increase in immunoreactive CCK concentration to 10±1.32 ng. A slower phase of GE followed at the rate of 0.19ml/mint, with EF of 90% at 10 minutes. The latter phase of GE was accompanied by a plateau CCK concentration at 9.5±1.5 ng/L. Sham feeding stimulated GE in two individuals (EF of 25% at 90 minutes) who both exhibited increase of plasma CCK concentration to 13±5ng/L. Subjects who did not exhibit GE had no such increase in CCK. Gastric distension was not followed by GE and CCK concentration did not increase.

Early GE was accompanied by an increase in plasma CCK. This is unlikely to be due to entry of nutrients into the small bowel or to gastric distension. With sham feeding, some individuals showed a cephalic phase of GE which was associated with CCK. These observations suggest that 'central' rather than intestinal factors are important in CCK release and early GE.

THE RELATIONSHIP BETWEEN LARGE BOWEL TRANSIT TIME (LBTT) AND THE PROPORTION OF DEOXYPHOSPHOCHOLIC ACID (%DCA) IN SERUM.

Gastroenterology Unit, Guy’s Campus and Mass Spectrometry Laboratory, St Thomas’ Campus, UMDS, London and the Depts of Endocrinology, St Bartholomew’s Hospital, London† and The Radcliffe Infirmary, Oxford.

Background: Prolongation of intestinal transit and an associated increase in the %conjugated DCA in gallbladder (GB) bile have been implicated in the pathogenesis of cholesterol gallstones. Since there is a dynamic exchange between the bile acid pools in the serum and bile, measurement of serum DCA levels provides a simple, non-invasive way of measuring the %DCA in total bile acids. Moreover, there are few data on the relationship between %unconjugated DCA in serum and LBTT — important since unconjugated DCA in serum represents newly formed secondary bile acids, absorbed from the colon.

Methods: We, therefore, measured large bowel transit time (LBTT), by a radiopaque marker shape technique, in a heterogeneous group of individuals (n=32, age range 22-67, 15 women), selected in anticipation of a wide range of spontaneous variations in LBTT, and the %DCA in the unconjugated and conjugated fractions of fasting serum, by gas chromatography-mass spectrometry. We then calculated the correlation coefficients (r) for the plots of LTBT against (%unconjugated DCA (b) % unconjugated DCA and %DCA (c) in total serum bile acids.

Results: The mean LBTT was 47±5(5)h (range 2-72h). The mean %DCA in the unconjugated serum bile acids was 31±3.2% (range 2-71%) and in the conjugated serum bile acids, 19±2.1% (range 3-52%). There were significant linear relationships between LBTT and %DCA in both the unconjugated (r=0.74, p<0.0001) and the conjugated (r=0.82, p<0.0001) fractions, and also between LBTT and the %DCA in the total serum bile acids (r=0.80, p<0.001).

SUMMARY: Unpublished results suggest a direct relationship between large bowel transit time and both the %unconjugated and conjugated DCA in serum and, therefore, by implication the %unconjugated DCA in GB bile. This suggests that changes in intestinal transit alter the bile acid profile in GB bile and, therefore, the risk of gallbladder stone formation.