T70

GUT LUMINAL NEUTROPHIL MIGRATION DEPENDS ON THE ANATOMICAL SITE OF CROHN’S DISEASE. E.R. Amiot, H.Drummond, L.Hardy, S.Ghosh, A.Ferguson. Gastrointestinal Unit, Department of Medicine, Western General Hospital, Edinburgh EH4 2XU.

Background: Gut luminal neutrophils can be studied by using whole gut lavage fluid (WGLF) obtained after bowel cleansing by a polyethylene glycol-electrolyte solution (Klean-Prep, Norgine). Cytology or an enzyme-substrate reaction to detect granulocyte elastase (SIN) can be performed on uncentrifuged WGLF. The chemotactants responsible for luminal neutrophil migration are unknown, but bacterial products are potential candidates.

Methods: 70 patients with well characterised active CD underwent whole gut lavage. The clear fluid obtained after complete gut cleansing was stored at -70°C. GE was assessed using the specific chromogenic substrate L-Prolylglutaminyl-L-prolyl-L-valine-p-nitroanilide (Quadratech, Epoxon). The lower limit of detection by this assay was 39 nkat. Patients were divided into 6 groups according to the distribution of macroscopic disease.

Results: 21 of 31 patients with Crohn’s colitis had detectable GE, (median 238, range <39-2742 nkat), whereas only 1 out of 10 patients with small bowel involvement had detectable GE (median <39, range <39-215 nkat; P<0.005 vs colonic disease). 10 out of 13 patients with both small bowel and colonic disease had detectable GE (median 180, range <39-1708 nkat; P<0.02 vs small bowel). In the 6 patients with recurrent small bowel disease who had prior ileocaecal resection, 5 had detectable GE, and the concentrations were significantly higher (median 228, range <39-1240 nkat) than in those with small bowel disease but no resections (p <0.05). 6 patients with an ileostomy and 4 patients with pelvic disease alone had undetectable GE. 4 of 5 patients with Crohn’s colitis who had received long-term low-dose corticosteroid therapy for possible tropical sprue before his diagnosis was established - had no detectable GE in lavage fluid. A high GE concentration of 548 nkat, was detected in a patient with small bowel CD, who had received high dose long-term NSAIIDs for relapsing spondylitis.

Conclusion: Neutrophil migration into the lumen of the gut is a feature of colonic but not small bowel Crohn’s disease suggesting that bacterial flora-derived neutrophil chemotactants may play a role in gut neutrophil migration. This hypothesis is further supported by the high GE concentrations found in recurrent small bowel disease after ileocaecal resection.

T71

GRAFT INFILTRATING LYMPHOCYTES IN LONG TERM LIVER TRANSPLANTS. A MARKER OF TOLERANCE? T. Wong, K. T. Nouri-Aria, J. Devlin, B. Portmann, Roger Williams. Institute of Liver Studies, King’s College School of Medicine and Dentistry, London SE5 9RS.

Clinical tolerance is present in a significant proportion of long term liver transplant recipients, although to date it has not been possible to reliably identify these recipients by conventional clinical, or biochemical, parameters. The present study examined whether immunohistochemical analysis of pre-weaning liver biopsies could discriminate unique patterns in patients subsequently found to be tolerant.

Methods: 37 biopsies: 27 from patients with stable graft function 5 years, or more post transplant, and 10 from patients experiencing acute rejection were studied. Anti-CD3, CD4, CD45RO, CD45RA, CD56, and CD68 staining was performed.

Results: Of the 27 long term patients, 20 subsequently underwent weaning of their immunosuppression; 6 were tolerant, 5 achieved substantial reductions in their immunosuppression (partially tolerant), and 9 were unable to achieve any substantial reduction (intolerant).

Reduced numbers of lobular CD8+ and CD3+ cells were present in the tolerant as compared to the intolertant grafts (median 15 vs 22 p<0.01, 15 vs 26 cells/high powered field [hpf] respectively, p<0.05). Similarly, there were fewer numbers of lobular CD3+, CD8+, CD45RO+ cells in tolerant grafts when compared with acute rejection (16 vs 32 p<0.01, 15 vs 31 p<0.01, 17 vs 24 p=0.03 median cells/hpf respectively). Unexpectedly more lobular CD45RO+ were present in tolerant when compared with partially tolerant patients (17 vs 10 mean cells/hpf, p<0.05).

Conclusions: In all long term liver grafts, infiltrating lymphocytes are present, and with those grafts from patients intolerant of immunosuppression withdrawal they are phenotypically similar to those during acute cellular rejection. Fewer CD8+ positive cells correlate with graft tolerance, and may aid in the identification of patients in whom successful withdrawal of immunosuppression may be undertaken.

T72

MONITORING OF LIVER OXYGENATION BY NEAR INFRARED SPECTROSCOPY.

Oobeide S, Seifalian AM, Doctor N, Javed M, Davidson BR University Dept of Surgery, Royal Free Hospital and Medical School, London.

Adequate oxygenation of the liver is fundamental to the outcome of liver surgery and orthotopic liver transplantation (OLT). Near Infrared Spectroscopy (NIRS) is a novel technique which can non-invasively measure tissue oxy(HbO2), deoxy(Deoxy Hb) and total haemoglobin(THb). The results of NIRS on the liver have not previously been compared with blood flow.

Large Landrace pigs (n=7) underwent laparotomy under general anaesthesia. Electromagnetic flowmeters were placed around the portal vein and hepatic artery and the NIRS probes on the surface of the right lobe. NIRS and flow were recorded continuously. Baseline readings were taken on achieving a steady state and subsequent recordings following occlusion of the hepatic artery (HA), portal vein (PV) and both (HA and PV) simultaneously.

The correlation between NIRS and hepatic blood flow is shown.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HA clamp</th>
<th>PV clamp</th>
<th>HA &amp; PV clamp</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbO2 (μmol/l)*</td>
<td>-27 ± 2</td>
<td>-185 ± 104</td>
<td>-226 ± 92</td>
</tr>
<tr>
<td>Deoxy Hb (μmol/l)*</td>
<td>-6 ± 6</td>
<td>-36 ± 48</td>
<td>-54 ± 40</td>
</tr>
<tr>
<td>HA (ml/min)*</td>
<td>0</td>
<td>178 ± 128</td>
<td>0</td>
</tr>
<tr>
<td>PV (ml/min)*</td>
<td>817 ± 191</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Changes relative to baseline. * values are in means±SD.

The baseline HA and PV blood flow were 148±110 and 741±170 ml/min. THb showed a strong correlation with total hepatic blood flow (r=0.932, p<0.001).

We would conclude from this study that NIRS would be an accurate non invasive method of assessing organ perfusion and oxygenation in patients undergoing liver resection or transplantation.
PROSPECTIVE STUDY OF HUMAN HERPES VIRUSES 6 AND 7 IN 50 LIVER TRANSPLANT PATIENTS CP Beaumont, PD Griffiths, K Rolles, AK Burroughs. Liver Transplantation, Royal Free Hospital, Pond St, London NW3 2QG.

Cytomegalovirus (CMV) infection is a cause of serious morbidity and mortality post-liver transplant. The significance of human herpes virus (HHV)-6 and HHV-7 is less well defined. The aim of this study was to investigate the incidence of these viruses and to determine their importance in 50 patients, studied prospectively, post-liver transplant using polymerase chain reaction (PCR) (Figure 1). The median time to firm PCR positivity was 36d for CMV, 20d for HHV-6 and 27d for HHV-7. Only 9% of samples were PCR positive for more than three consecutive days.

Figure 1: Betal hsv strains in liver transplant virus patients on a per patient and per sample basis. Patients with CMV had a median [range] of 40[0-9] biopsies samples in which detection was significantly greater than the patients without CMV (20[0-4]). There was a trend for increased rejection episodes in patients with HHV-6 infection (31-9); p=0.057). The CMV group had significantly more febrile episodes above 37.5°C (91-55) compared with the group without CMV (30-34); p=0.019). The CMV group had significantly greater total hospitalisation (5432-3214) compared with the non-CMV group (922-2154); p=0.0018) and the HHV-6 group had significantly greater subsequent hospitalisation after the initial hospital stay (2611-155) compared with the group without HHV-6 (1530-164); p=0.0029). For HHV-7 there was no apparent association with length of hospitalisation, febrile episodes or rejection episodes. This study has investigated the significance of 2 new herpes viruses in immunocompromised patients post liver transplant. The results demonstrate that HHV-6 and HHV-7 infections occur in these patients and suggest that HHV-6, but not HHV-7, may be an important pathogen in addition to CMV.

KUPFFER CELL ACTIVATION DURING THE PROGRESSION OF HEPATIC INJURY. AJ Makin, KC Thompson*, J Gentry*, RD Hughes, N Sherson*, Roger Williams Institute of Liver Studies, King's College Hospital, London SE5 9RS, *University of Southampton, Southampton.

Kupffer cells (KC) produce vasoactive cytokines and prostanoids which may be a pivotal event in the response to hepatic injury. The aim of this study was to determine the production of these mediators by KC during the development and progression of hepatic inflammation. Methods: Hepatic injury was induced in rats by galactosamine (1.1 g/kg, i.p.) and the production of proinflammatory mediators in KC was determined by centrifugal elutriation. Controls were untreated controls. By 24h, KC had increased to 39% of control values. By 24h, phagocytosis had decreased to 39% of control values and remained below control values until 72h. Peak O2 production, 85% compared to controls (p<0.05), was observed at 24h and remained significantly elevated until 48h. Peak KC TNF production was observed by 12h and IL-1, IL-6 and PGE2 production were all maximal at 48h. At 72h cytokine, PGE2 and O2 production were significantly reduced.

Conclusions: Following a hepatoxic insult KC function changes as hepatoxical damage progresses. The sequential and differential production of these mediators may be an important factor in the progression of liver damage and the development of systemic changes associated with severe liver injury.

T75

HLA DR4 AND DR4 SUBTYPES CONFER RESISTANCE TO PRIMARY SCLEROSING CHOLANGITIS AND ARE NOT ASSOCIATED WITH A POOR PROGNOSIS. MM Moloney, EE Donaldson, LJ Thomsen, and Roger Williams. Institute of Liver Studies, King's College Hospital, London SE5 9RS, U.K.

There is a consensus that HLA DRB1*0301 is associated with an increased risk of developing PSC, but the role of DR4 is disputed. Early data from our series suggested that DR4 may have a protective effect though a similar study from Sweden suggested that DR4 is neutral, and a second study of British patients suggested that DR4 is associated with a poor prognosis. The aim of this study was to reassess the role of HLA DR4 and the DR4 subtypes DRB1*0401 to DRB1*0408 in PSC. We have determined the HLA genotypes in 114 PSC patients and 48 healthy controls using a standard PCR protocol. HLA DRB1*0301 was significantly increased in patients compared to controls (64% versus 26%; p=0.0054, RR = 2.37). Only 16 patients (14%) had DR4 compared to 54/134 controls (40%; p=0.0002, RR = 0.24), though DR4 subtyping revealed that this was not caused by the complete absence of any particular DR4 allele. To determine whether the negative association with DR4 is simply due to the over-representation of DRB1*0301 we re-analysed the distribution of DRB1 alleles in the DRB1*0301 negative patients and controls. Only 12/62 (19%) of DRB1*0301 negative patients were DR4 positive compared with 46/99 controls (47%; p = 0.0015, RR = 0.28). To test the hypothesis that DR4 may be associated with a poor prognosis in PSC we analysed the survival of patients from presentation to the end points of death or liver transplantation. There was no difference in survival between those with and without DR4 either in median survival times (94 versus 98 months) or as determined by Kaplan-Meier curves. In conclusion: DR4 is associated with resistance to PSC and the association is not simply a statistical quirk caused by the over-representation of DRB1*0301. However, in contrast other reports from the U.K., DR4 is not associated with poor prognosis.

A biallelic polymorphism has been described at position -308 in the TNF alpha promoter region. The less common allele (known as TNF F) has been reported to modulate mediator transcription of TNF alpha in vitro. TNF suppresses HBV replication and higher TNF levels are found in patients who clear chronic hepatitis B infection following interferon treatment. On the other hand, TNF is reported to inhibit the expansion of virus-specific CD8 cells. We have explored the possibility that the TNF 2 allele might influence susceptibility to persistent HBV infection.

507 samples came from a large case-control study of childhood severe malaria in The Gambia and were classified for HBV serologically: persistent infection was defined as HBsAg positive, anti-HBc total, anti-HBc(positive), and previous transient infection as anti-HBc total, positive, HBsAg negative (n = 399). The TNF 2 allele was typed by PCR using genomic DNA extracted from peripheral blood. MHC class II types were analysed by restriction fragment length polymorphism.

In the persistently infected group, there were 7 (4.1%) homoygotes for TNF2 and 54 (32.1%) heterozygotes, compared to 10 (2.9%) homoygotes and 43 (12.7%) heterozygotes in the transiently infected group. In analysing these data it was necessary to stratify for HLA DRB1*1302, which is associated with HBV clearance and is in linkage disequilibrium with the TNF 2 allele in this population. After stratification the odds ratio for persistent infection in subjects with the TNF2 allele was 1.56 (95% confidence interval 1.03 - 2.38). When children with severe malaria (associated with TNF2) are excluded from the analysis the odds ratio for persistent infection for subjects with TNF2 allele is 1.03 (95% confidence interval 0.47 - 2.39).

In conclusion, we find that the TNF 2 allele is associated with an approximately 2 fold increased risk of persistent HBV infection. This may be caused by disregulation of TNF expression and its effect on the maintenance of tolerance to viral antigens.
A MULTISPECIFIC T LYMPHOCYTE RESPONSE TO HEPATITIS C VIRUS PROTEINS IS FOUND IN PATIENTS WITH VIRAL CLEARANCE. ME Camp, P Carucci, S Chokshi, S Rossol, PT Donaldson, Roger Williams, NV Naoumov Institute of Liver Studies, King’s College Hospital, London, SES 9RS.

A minority of those infected by hepatitis C virus (HCV) will clear the infection spontaneously, but how they do so is not clearly understood. The aim of this study was to compare whether the CD4+ T lymphocyte response to a variety of HCV proteins differs in those with apparent immunity and those with HCV related liver disease.

Method: We studied 3 groups I) 26 HCV antibody positive but repeatedly HCV RNA negative patients without any evidence of liver disease; II) 14 anti-HCV and HCV RNA positive patients with persistently abnormal ALT and biopsy proven chronic hepatitis C; III) 9 healthy controls. Groups I and II were comparable in terms of age, sex, and route of infection. Where possible, duration of infection was estimated - median of 16 years for both groups (range 6-29 in group I and 5-21 in group II). The peripheral CD4+ T lymphocyte response to the HCV proteins NS3, NS4 and core was tested by proliferation assay ('N-thymidine uptake) with a stimulation index of > 3 considered significant. Serum HCV RNA was sought by Amplicor assay (Roche).

Results: A T lymphocyte response to any of the HCV proteins was detected in 14/26 negative patients, compared to only 2/14 of the RNA positive patients (p=0.0016). 12/26 RNA negative patients had a multispecific response to more than one antigen, whereas none of the 14 RNA positive patients did (p = 0.0017). All 9 healthy controls responded to tetanus toxoid but none to any of the HCV proteins tested.

Conclusions: A strong and multispecific T lymphocyte response to HCV proteins was only found in those HCV infected patients who had successfully cleared the virus and is maintained for many years after initial exposure to HCV, raising the possibility of continuing immunostimulation by viral proteins from hidden reservoirs of infection.

HLA STATUS AND SEVERITY OF CHRONIC HEPATITIS C VIRUS INFECTION. CS Blain1, GH Hayden1, M McColl2, PM Yap3, PC Hayes1. Department of Medicine1 and Scottish National Blood Transfusion Service2, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh, UK.

The natural history of chronic hepatitis C virus (HCV) infection appears highly variable with a significant minority of those infected developing cirrhosis within 20 years, whilst others appear to escape longterm complications. In this study we examined the role of host HLA class I and II in determining both the severity and progression of chronic hepatitis C infection.

Methods: 71 (41 male) consecutive patients RT-PCR positive for HCV RNA were included in the study. Each patient was typed for HLA class I and II, and A, B, and DR using a two stage complement-dependent microlymphocytotoxicity technique. Comparison between HLA allele frequencies in the HCV infected population and a population of healthy normal controls was performed by chi-squared analysis. Intra-population variation was assessed both between patients with histologically proven cirrhosis and those with chronic hepatitis, and those with persistently normal or abnormal transaminases (ALT).

Results: 17 (24%) patients had biopsy proven cirrhosis following liver biopsy. 13 out of 54 (24%) patients with chronic hepatitis had a normal ALT value. In the control Scottish population, commonly expressed HLA loci were A1,2,3,4,11,24, B7,8,35,44 and DR(1,2,3,4,5,6,7). The frequencies of HLA loci A1 and DR5 were significantly higher in the normal population compared with chronically infected individuals (p=0.02 and p<0.001). Likewise, the frequencies of HLA B8, B35 and DR6 occurred significantly more frequently in chronic hepatitis compared with hepatitis cirrhosis (p=0.02, p=0.002 and p=0.004). A1 and DR5 were associated with persistently normal transaminases (p=0.04 and p=0.003) and B7 and DR7 with abnormal transaminases (p<0.0001 and p<0.0001).

Conclusions: In chronic HCV infection, certain commonly occurring HLA loci may protect individuals against chronicity of infection, progression to cirrhosis and significant hepatic inflammation.


HCV Ab testing by 2nd and 3rd gen. enzyme immunoassay (EIA) has a low positive predictive value in low risk populations and should be confirmed with supplemental testing. Indeterminate serology then frequently arises, the cause and appropriate management is unclear.

Methods: 100 patients with equivocal HCV serology were identified. These patients had initial EIA (+) (Abbott 2.0 or 3.0) but RIBA (Ortho 2.0 or 3.0) negative (no bands) or indeterminate (1 band positive). All patients were questioned re possible parental risk factors. LFTs were performed on at least 3 occasions. HCV RNA was performed in 47 using Roche Amplicor kit. Liver biopsy was done in 16 patients (15 with abnormal LFTs). Patients were classified into 2 groups: I - RIBA negative, II - RIBA indeterminate.

Results: Group I =39 (%) Group II =61 (%)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA positive</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HCV RNA negative</td>
<td>36</td>
<td>51</td>
</tr>
<tr>
<td>Abnormal ALT</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Biopsy not HCV</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Biopsy positive HCV</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>
# includes 4 patients identified by transfusion 'look-back' program as receiving transfusions from HCV Ab (+) donors. *Chi-square analysis.

Summary: Patients with indeterminate RIBA were significantly more likely to have a parental risk factor for HCV compared to those with negative RIBA. This is consistent with indeterminate RIBA sometimes resulting from previous exposure to HCV, as seen in the 4 patients exposed to HCV by contaminated blood transfusion. The majority of such patients however have normal LFTs and neg. PCR, suggesting resolved HCV.

The frequent finding of indeterminate serology in healthy populations indicates that spontaneous resolution of HCV may be underestimated in determination of the natural history of HCV. Host immune responses in such subjects should be studied. Patients with equivocal HCV serology are a heterogeneous group with many possible explanations; ‘séro-reversion’ is one possible cause.
**T81**

**ASYMPTOMATIC BLOOD DONORS WITH CHRONIC HEPATITIS C BENEFIT FROM ALPHA-INTERFERON THERAPY.** D Thorburn, GLA Bird, E Spence, EAB McCruden*, D Frame*, RMN MacSween*, and PR Mills. Gastroenterology Unit, *Institut National de ve Peau et Velo, **University Department of Pathology, Western Infirmary, Glasgow and *West of Scotland Blood Transfusion Service, Law Hospital, Wishaw.

**Introduction:** The management of asymptomatic blood donors with chronic hepatitis C virus (HCV) infection remains uncertain. Whether they would benefit from or tolerate alpha-interferon (IFN) remains untested. A randomised study was designed to answer these questions.

**Patients & Methods:** 40 asymptomatic blood donors with HCV infection (ELISA and RIBA positive) and chronic hepatitis on liver biopsy were randomised into two groups: a treatment group (n=20) who received decreasing IFN (4.5MU-1.0MU) t.i.w. for 48 weeks and an observation group (n=20) who were untreated. Both groups had monitoring of serum ALT levels and HCV-RNA at intervals of 12 weeks to 72 weeks and liver histology graded at baseline and 48 weeks.

**Results:** In the treatment group 10 (53%) of 19 HCV-RNA positive patients had a complete biochemical and virological response by 12 weeks which was sustained in 5 (26%) to 72 weeks. Four had a breakthrough in ALT on treatment, 2 withdrew and 4 had no biochemical response to therapy. In the treatment group low baseline ALT predicted a sustained response to IFN (mean ± SD 72±53 v 132±65, p<0.02).

**Conclusions:** Asymptomatic blood donors tolerate IFN therapy and their response rates are comparable, if not better, than other patient groups with chronic hepatitis C.

**T82**

**NEW CLUES TO THE FUNCTIONAL RENAL FAILURE IN HEPATORENAL SYNDROME (HRS) AND ITS EVOLUTION TO ACUTE TUBULAR NECROSIS (ATN).** P. Jayal, J Yates, S. Grimes*, M. Critchley*, K.P. Parsons, & S.A. Jenkins. Departments of Urology and Nuclear Medicine*, Royal Liverpool University Hospital. Liverpool.

Renal failure complicates the course of advanced liver disease in >40% of patients. This renal failure is thought to be functional in nature and termed as HRS. But patients with liver disease develop classical ATN as frequently as HRS. **99mTc MAG3** is primarily excreted by tubular secretion and therefore may serve as a sensitive marker for renal tubular function. We investigated the efficacy of **99mTc MAG3** renal clearance and extraction fraction in determining HRS and ATN in an experimental setting.

Liver failure was induced in male Wistar rats by administration of 1.1g/kg D-Galactosamine. Parameters assessed at 42 and 48 hours included: Serum(S) urea and creatinine, **99mTc MAG3** clearance and renal extraction fraction(E.F.) ([Gamma] camera based Peters first pass integration technique and Patlak plot), urinary (U) sodium and urinary osmolality and liver function tests.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clearance</th>
<th>E.F.</th>
<th>S.Creatinine</th>
<th>U.Sodium</th>
<th>U.Osmol.</th>
<th>mmol/l</th>
<th>mmol/l</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>55±1+46</td>
<td>1.99±20</td>
<td>26.3±2.2</td>
<td>128.4±2.2</td>
<td>278.8±2.1</td>
<td>1.5±0.6</td>
<td>30±10</td>
<td>15±0</td>
<td>10±0</td>
</tr>
<tr>
<td>42 hours</td>
<td>105±1+73</td>
<td>1.35±20</td>
<td>24.9±2.4</td>
<td>127.2±5.4</td>
<td>275.2±4</td>
<td>1.5±0.6</td>
<td>30±10</td>
<td>15±0</td>
<td>10±0</td>
</tr>
<tr>
<td>48 hours</td>
<td>115±2+76</td>
<td>0.50±2</td>
<td>4.5±2.6</td>
<td>142±3±6.7</td>
<td>298±6±25</td>
<td>1.5±0.6</td>
<td>30±10</td>
<td>15±0</td>
<td>10±0</td>
</tr>
</tbody>
</table>

Liver failure at 42hours was associated with a significant increase in serum urea, creatinine and oliguria, *i.e.* features of renal failure, but avid urinary sodium reabsorption and high urinary osmolality was accompanied by unchanged **MAG3** clearance and E.F., this was indicative of functional renal failure. At 48hours there was a significant (p<0.002,ANCOVA) decrease in **MAG3** clearance and E.F.; furthermore, urinary sodium concentration was high and urinary osmolality low, this was indicative of ATN.

The results of this study suggest that 1) renal failure in HRS is functional and can be predicted by **MAG3** clearance and E.F. 2) HRS and ATN in liver failure form a continuum rather than being different diseases.

**T83**

**ENHANCED PORTAL PRESSURE RESPONSE TO ETHANOL IN CIRRHOTIC RATS: THE ROLE OF ENDOTHELIN.** Richard Marley, David Harry, Bimbi Fernando and Kevin Moore. Dept. of Medicine, Royal Free Hospital, London, UK.

**Background & Aims:** Variceal bleeding in the context of alcoholic liver disease often follows heavy drinking. The effect of ethanol on portal pressure has been well documented in normal rats, but not in cirrhotic animals. In this study the effect of ethanol inflation was compared between normal and cirrhotic ( bile duct ligated) rats and the effect of endothelin receptor blockade on the response to ethanol was examined.

**Methods:** The livers from normal and cirrhotic rats were perfused in vitro with Krebs Henseleit buffer and the portal pressure response to ethanol either alone or in the presence of an ET-A or ET-B receptor antagonist was monitored.

**Results:** Infusion of ethanol increased portal pressure in both normal and cirrhotic groups, with a significantly greater response in cirrhotic rats. At a final infusion concentration of 100 mmol/l (c.f. legal driving limit ~ 20 mmol/l, with portal blood concentrations being higher) mean portal pressure increased from a baseline of 9.4±0.5 mmHg to 13.1±1.6 mmHg in normal rats (p<0.05), whereas in cirrhotic animals portal pressure increased from 13.1±1.7 mmHg to 22.5±4.4 mmHg (p<0.01). In normal rats addition of either the ET-A receptor antagonist BQ 610 or the ET-B receptor antagonist IRL 2500 had no effect on the response to ethanol, however in cirrhotic rats the response was almost completely blocked by co-infusion with BQ 610.

**Conclusions:** This is the first demonstration that ethanol has a significantly greater effect on portal pressure in cirrhosis, and that this can be inhibited by an endothelin receptor antagonist, perhaps providing a novel avenue for treatment.

**This work was supported by the Medical Research Council, UK.**

**T84**

**COMPARATIVE EFFECTS OF DOPAMINE, OCTREOTIDE AND ORNIPRESSIN ON RENAL HAEMODYNAMICS IN LIVER FAILURE.** P. Jayal, J Yates, K.F. Parsons, and S.A. Jenkins. Department of Surgery and Urology, Royal Liverpool University Hospital, Liverpool.

Abnormalities in renal blood flow (RBF) and function in liver disease are believed to be closely related to alterations in hepatosplanchnic haemodynamics. Since vasoactive agents which alter hepatosplanchnic haemodynamics may improve RBF and hence function in liver failure, we have carried out a study to investigate this possibility in rats.

Liver failure was induced in male Wistar rats by administration of D-Galactosamine (1.1g/kg). The regional blood flow (microsphere method), intra-renal shunting (IRS) and portal systemic shunting (consecutive injections of **99mTc** methyl diprophosphate and **99mTc** albumin microspheres), portal pressure (PP) and arterial blood pressure were measured before and 20 min after i. 1) low dose dopamine (4micromg/kg/min), 2) high dose dopamine (16micromg/kg/min), 3) octreotide (4micromg/kg/h) and 4) ornipressin [8-ornithin vasopressin](0.043 IU/h).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RBF</th>
<th>IRS</th>
<th>SPS</th>
<th>PFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>%DCO</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Baseline</td>
<td>71±2.9</td>
<td>11±3±2.5</td>
<td>38±2±3.1</td>
<td>11±2±3.1</td>
</tr>
<tr>
<td>Post infusion</td>
<td>59±1±6.7</td>
<td>3±2±9.7</td>
<td>16±7±3.9</td>
<td>6±3±9.7</td>
</tr>
</tbody>
</table>

Following infusion of ornipressin there was a significant increase in RBF along with a decrease in intra-renal shunting and renal vascular resistance. These changes were accompanied by decreases in portal pressure, intrahepatic portal systemic shunting (PPS) and portal venous inflow (PFP). There were no significant changes following infusion of octreotide and high dose dopamine, low dose dopamine resulted in a marginal improvement in RBF without any significant change in the hepatic haemodynamics.

The results of this study suggest that ornipressin 1) improves renal haemodynamics possibly by reducing the pooling of blood in the hepatosplanchnic circulation and thus increasing the effective blood volume 2) is the vasoactive treatment of choice for functional renal failure in severe liver disease.
**Investigation into the Effects of FK506 (a Novel Adenosine-1 Receptor Antagonist) in Cirrhotic Patients with Ascites: A Pilot Study.**


*Dept. Medicine, Royal Infirmary of Edinburgh EH3 9YW.*

Cirrhotic patients have a characteristic hyperdynamic systemic circulation and evidence of renal vasoconstriction and tubular dysfunction, maximal in patients with ascites. These renal abnormalities are reproduced by stimulation of adenosine (ADO)-1 receptors in the kidney.

**Aim:** To assess the systemic and renal effects of a novel ADO-1 antagonist (FK506) in cirrhotic patients with ascites.

**Patients:** Eight cirrhotic patients (4 males) were studied (mean age 52.3 years (3.3), mean CFS 8.1 (0.5)). None were taking vasoactive medications and diuretics were stopped 1 week prior to the study.

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<tr>
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No changes were seen in CI or SVRI. Clearance results are awaited.

**Conclusion:** ADO appears to have a role in the renal impairment seen in cirrhosis, acting via ADO-1 receptors. ADO-1 specific antagonism offers a new therapeutic approach to the management of cirrhotic ascites and the associated renal dysfunction.

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**Paediatric Nutrition** T86–T87

**Basic Science** T88–T101

**Investigation into the Effects of FK506 (a Novel Adenosine-1 Receptor Antagonist) in Cirrhotic Patients with Ascites: A Pilot Study.**


*Dept. Medicine, Royal Infirmary of Edinburgh EH3 9YW.*

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