T90

Gut LUMINAL NEUTROPHIL MIGRATION DEPENDS ON THE ANATOMICAL SITE OF CROHN’S DISEASE

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Background: Gut luminal neutrophils can be studied by using whole gut lavage fluid (WLF) obtained after bowel cleansing by a polyethylene glycol-electrolyte solution (Klean-Prep, Norgine). Cytology of an enzyme-substrate reaction to detect granulocyte elastase (GNE) can be performed on concentrated WLF. The chemotactic agents 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 chromatographic substrate L-Prolylglutamyl-L-prolyl-L-valine-p-nitroanilide (Quadratech, Epsom). The lower limit of detection by this assay was 39 nkat/mL. Patients were divided in 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/mL), whereas only 1 out of 10 patients with small bowel involvement had detectable GE (median <39, range <39-215 nkat/mL; 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/mL; P<0.02 vs small bowel). In the 6 patients with recurrent small bowel disease who had prior ileocolonic resection, 5 had detectable GE, and the concentrations were significantly higher (median 228, range <39-1240 nkat/L) than in those with small bowel disease but no resections (P<0.05).

6 patients with an anomalous and a patient with perianal disease alone had undetectable GE. None of the patients with Crohn’s colitis had received long-term systemic therapy for possible tropical sprue before his diagnosis was established - he had no detectable GE in lavage fluid. A high GE concentration of 584 nkat/L was detected in a patient with small bowel CD, who had received high dose long-term NSAIDs 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 ileocolonic resection.

T91

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-Infra-Red Spectroscopy (NIRS) is a novel technique which can non-invasively measure tissue oxygen(HbO2), deoxyDeoxy Hb) and total haemoglobin(TbHb). 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).

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 (umol/l)</td>
<td>-0.27±0.23</td>
<td>-1.85±0.10</td>
<td>-2.26±0.92</td>
</tr>
<tr>
<td>Deoxy Hb (umol/l)</td>
<td>-0.26±0.24</td>
<td>-0.36±0.48</td>
<td>-0.84±0.40</td>
</tr>
<tr>
<td>HA (mmHg)</td>
<td>0</td>
<td>178±128</td>
<td>0</td>
</tr>
<tr>
<td>PV (mmHg)</td>
<td>0</td>
<td>178±128</td>
<td>0</td>
</tr>
<tr>
<td>Changes relative to baseline. * values are in mean±SD.</td>
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<td></td>
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</tbody>
</table>

The baseline HA and PV blood flow were 145±110 and 741±170 mmHg. 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.

T92

Inflammatory Bowel Disease: Strong Evidence for Susceptibility Loci on Chromosomes 3, 7 and 12

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Concordance rates in siblings and twin pairs have provided strong evidence that genetic predisposition is important in the pathogenesis of the inflammatory bowel disease (IBD). However, neither Crohn’s disease (CD) nor ulcerative colitis (UC) has a single Mendelian pattern of inheritance; the model which seems most pertinent to inflammatory bowel disease is that of a heterogeneous group of polygenic disorders. In the present study, a systematic two-stage search of the human genome for susceptibility genes in inflammatory bowel disease was performed, involving 186 affected sibling pairs.

In the first stage, 89 sibling pairs with IBD were genotyped at 260 microsatellite markers spanning the 22 autosomes, using fluorescent labelled primers for polymerase chain reaction, and semi-automated DNA fragment sizing technology. Allele sharing in affected sibling pairs provided evidence for linkage with 12 markers in 5 distinct regions of chromosomes 2, 3, 7, 12 and 15 (p<0.001 for an individual marker, or adjacent markers each with P<0.01).

In the second stage, a further 97 affected sibling pairs with IBD were genotyped; linkage for the clustered markers on chromosomes 3, 7 and 12 was confirmed.

Combining data from the first and second stages provided striking evidence for linkage with 3 adjacent markers on chromosome 3 (D3S1424, D3S1422, D3S1421) and 2 adjacent markers on chromosomes 7 (D7S658, D7S659) and 12 (D12S375, D12S378) (P<0.01 for each).

Combining data from the third stage, gene mapping was undertaken for chromosome 3 (the STRONG marker locus for susceptibility). Strong candidate genes are present in each of the regions which have been implicated, and are currently being studied.
PROSPECTIVE STUDY OF HUMAN HERPES VIRUSES 6 AND 7 IN 50 LIVER TRANSPLANT PATIENTS CP Barrett, 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 one virus.

Figure 1: Betaherpesvirus infections in liver transplant patients

Patients with CMV had a median [range] of 40-99 biopsies with rejection which was significantly greater than the patients without CMV (20-4) (p=0.0043 Mann Whitney U). 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 (64[33-321]d) compared with the non-CMV group (39[22-215]d, p=0.0018) and the HHV-6 group had significantly greater subsequent hospitalisation after the initial hospital stay (26[11-15]d) compared with the group without HHV-6 (13[50-164]d, 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-7, but not HHV-6, may be an important pathogen in addition to CMV.

T74

KUFFER CELL ACTIVATION DURING THE PROGRESSION OF HEPATIC INJURY. AJ Makin, KC Thompson*, J Gentry*, RD Hughes, N Sherer, S.Rogers, D. Williams Institute of Liver Studies, King's College Hospital, London SE5 9SR, and *University of Southampton, Southampton.

Kuffer 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 hepatocellular injury. Methods: Hepatic injury was induced in rats by galactosamine (1.1 g/kg, i.p.) following hepatic collagenase/propane peroxynitrite, KC were isolated by centrifugal elutriation from untreated (control) rats and at 12, 24, 48 and 72h post galactosamine injection. KC phagocytic activity was assessed by uptake of 1 μm latex beads and following phosphor myristate acid stimulation, superoxide anion (O₂⁻) production was measured by ferricytochrome c reduction. KC were cultured overnight and TNF, IL-1 and IL-6 formation measured by L929, D10(N4)M, and B9 biosassays respectively and PGE₂ production by ELISA. Results: Phagocytic activity of KC isolated from rats 2h post galactosamine increased by 212% (p<0.05) from 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 still significantly greater than controls. Conclusions: Following a hepatotoxic insult KC function changes as hepatocellular 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.

T76

TNFα PROMOTER POLYMORPHISM AND THE OUTCOME OF HBV INFECTION

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A biallelic polymorphism has been described at position -308 in the TNF alpha promoter region. The less common allele (known as TNF 2) has been reported to be associated with sepsis and liver failure.

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) positive, anti-HBc (core) negative and previous transient infection as anti-HBc (total) positive, HBsAg negative (n=339). 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%) homoyzygotes for TNF2 and 54 (32.1%) heterozygotes, compared to 10 (2.9%) homoyzygotes and 43 (12.7%) heterozygotes in the transiently infected group. In analysing these data it was not significant for HHV-1.

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 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 ('H-thymidine uptake) with a stimulation index of > 3 considered significant. Serum HCV RNA was sought by Amplicor assay (Roche).

Results: A CD4+ T lymphocyte response to any of the HCV proteins was detected in 14/26 HCV negative patients, compared to only 2/14 of the RNA positive patients (p=0.016). 12/26 RNA negative patients had a multispecific response to more than one protein, whereas none of the 14 RNA positive patients did (p = 0.0017). All 9 healthy controls responded to taxans toxoid but none to any of the HCV proteins tested.

Conclusions: A strong and multispecific CD4+ 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.

Several studies have suggested the presence of HCV in peripheral blood mononuclear cells (PBMC's), but it remains unclear which cell subsets HCV infects. The objective of this study was to confirm that HCV can be detected in PBMC's and then to study the cellular tropism of HCV by analysing different subsets of PBMC's for evidence of HCV infection in patients chronically infected with HCV. The presence of replicating HCV in lymphoid cells was determined by the detection of HCV RNA in liver derived lymphocytes cultured from liver biopsy specimens with polyclonal T-cell stimulation for at least 4 weeks.

The majority of patients (8/9 serum +ve patients) had HCV detectable in total PBMC populations. HCV was not detected in the CD4 cell subset (9/18) but was found in CD8 positive T lymphocytes (6/17), monocyte/macrophages (3/8) and CD19 positive B lymphocytes (4/6). All cell samples were washed at least four times prior to cell culture to ensure that all extraneous HCV RNA was always negative. Liver derived lymphocytes were kept in long term culture from two patients. Cell lines cultured for more than 4 weeks containing CD4 positive, CD8 positive and CD4/CD8 negative cells were established with detectable HCV RNA by PCR.

In conclusion most chronically infected patients have HCV associated with the total peripheral mononuclear cells. No patient had HCV associated with the CD4 cell population but HCV was found in the CD8, monocyte/macrophage and B cell populations. Whether the positive PCR signals from these cell populations represents active 3rd generation infection remains unclear. In the absence of a reliable method for the detection of replication. However the presence of HCV RNA from cells kept in long term culture suggests that HCV does replicate non-cytopathically in lymphoid cells.

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 A, B and DR using a two stage complement-dependent microlymphotoxicity 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 transaminites (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 A(1,2,3,11,24), B(7,8,35,44) and DR(1,2,3,4,5,6,7). The frequencies of HLA loci A11 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 hepatic cirrhosis (p=0.02, p=0.002 and p=0.004). A1 and DR3 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.

WHAT IS THE SIGNIFICANCE OF INDETERMINATE HEPATITIS C SEROLOGY? B.C. Smith, M.F. Fassbendine, Dept of Medicine, University of Newcastle, England

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 parenteral 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: 1 - RIBA negative, 2 - RIBA indeterminate.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Group I =39 (%)</th>
<th>Group II =61 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td>10</td>
<td>30 # p&lt; 0.05*</td>
</tr>
<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>20</td>
<td>10</td>
</tr>
<tr>
<td>Biopsy positive</td>
<td>10</td>
<td>7</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 parenteral 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 McCrum*, D Frame*, RNM MacSween*, and PR Mills. Gastroenterology Unit, *Institute of Virology, +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 to two groups: a treatment group (n=20) who received decreasing IFN (4.5MU-1.0MU) 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 73±53 v 132±55, p=0.02).

Necroinflammatory activity on liver biopsy improved in the treatment group showing complete response (median grade 4 v 2, p=0.03). The observation group showed no significant change in any parameter over 48 weeks.

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).


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. Patients with liver disease develop classical ATN as frequently as HRS. 59mTcTOMAG3 is primarily excreted by tubular secretion and therefore may serve as a sensitive marker for renal tubular function. We investigated the efficacy of 59mTcTOMAG3 renal clearance and extraction fraction in differentiating 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, 59mTcTOMAG3 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.

Conclusions: 1) Baseline Clearance of U.Sodium and U.Osmol is significantly different in rats with hepatorenal syndrome compared to those with acute renal failure. 2) Infusion of ornipressin in rats with hepatorenal syndrome resulted in a significant increase in renal blood flow when compared to low dose dopamine resulted in a decrease in renal blood flow and renal vascular resistance. These changes were accompanied by decreases in portal pressure, intrahepatic portal systemic shunting and portal venous inflow. This suggests that ornipressin may be a useful tool in the management of hepatorenal syndrome.

**T83**

ENHANCED PORTAL PRESSURE RESPONSE TO ETHANOL IN CIRRHOTIC RATS: THE ROLE OF ENDOTHELIN.

Richard Marley, David Harper, Binibi 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 infusion 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 ETA- 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 Jayla, 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 hepato-splanchnic haemodynamics. Since vasoactive agents which alter hepato-splanchnic 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 59mTe methyl-diprophosphonate and 99mTc-albumin microspheres], portal pressure (PP) and arterial blood pressure were measured before and 20 min after infusion of: 1) low dose dopamine (4microgm/kg/min), 2) high dose dopamine (16 microgm/kg/min), 3) octreotide (4microgm/kg/h) and 4) ornipressin (8-ornithin vasopressin) (0.043 IU/h).

Conclusions: 1) 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 (PSS) and portal venous inflow (PVI). 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 hepato-splanchnic 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.**

*AJ Stanley, EH Forrest, KI Dubois, PC Hayes.*

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 CPS 8.1 (0.5)). None were taking vasoactive medications and diuretics were stopped 1 week prior to the study.

**Methods:** Urine and plasma were collected at half hourly intervals for 2 hours before and 2 hours after administration of 10mg (first 4 patients) or 25mg FK506 (next 4 patients) to measure absolute sodium excretion (Ur. Na), free water clearance (H2O Cl) and estimate GFR and renal plasma flow (RPF) using insulin and PAH clearance methods. Unilateral renal vein flow (RBF) (thermodilution method), cardiac index (CI) and systemic vascular resistance index (SVRI) were measured prior to and following drug administration.

**Results:** Pre and post drug administration results are summarised:

<table>
<thead>
<tr>
<th></th>
<th>Ur. Na (umol)</th>
<th>Ur. volume (ml)</th>
<th>H2O Cl (ml/min)</th>
<th>RBF (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>209.7 (106.5)</td>
<td>207 (85.3)</td>
<td>3.8 (1.2)</td>
<td>451.7 (146.5)</td>
</tr>
<tr>
<td>Post</td>
<td>549.0 (159.5)</td>
<td>392 (58.4)</td>
<td>7.9 (2.2)</td>
<td>580.9 (154.3)</td>
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<tr>
<td>p value</td>
<td>&lt;0.01</td>
<td>p=0.02</td>
<td>p=0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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**

**Efficacy and Safety of Supplementary Nasogastric Feeding in Children Undergoing Bone Marrow Transplantation.**

A Papadopoulos, A McDonald*, MD Williams*, PJ Darbyshire*, JW Booth

Institute of Child Health, University of Birmingham and *The Childrens Hospital, Birmingham

Nutritional insult following bone marrow transplantation is complex and its nutritional management challenging. Enteral nutrition (EN) is cheaper and easier to provide than parenteral nutrition, but its tolerance and effectiveness in reversing nutritional depletion following BMT is poorly defined. We therefore prospectively assessed nutritional status, well being and nutritional biochemistry in 21 children (mean age 7.5 years; 14 males) who received nasogastric feeding following BMT (mean duration of 17 days) and in 8 children (mean age 8 years, 4 males) who refused enteral nutrition and who received dietetic advice only. Results: Enteral nutrition was stopped prematurely in 6 patients. Greater increases in weight (p=0.0005), and mid arm circumference (p=0.01), were observed in the EN group, while positive correlations were found between the duration of feeds and improvement in weight (r=0.75; p=0.0001), and in mid arm circumference (r=0.74; p=0.0004). Vomiting, diarrhoea and fever were not more frequent in the EN group, while febrile episodes and diarrhoea tended to have a quicker duration than in the dietetic counselling group (p=0.05 and p=0.06, respectively). Diarrhoea occurring during EN was not associated with fat malabsorption, while carbohydrate malabsorption was associated only with rotavirus infection. However, enteral feeding did not affect bone marrow recovery, hospital stay, the general well-being of patients, or serum albumin concentration. Hypophosphataemia, zinc and selenium deficiency were common in both groups. In conclusion, enteral nutrition when tolerated is effective in reversing nutritional insult following BMT. With existing regimens nutritional biochemistry should be closely monitored in order to provide supplements when required.

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**Basic Science**

**T88-T101**

**Gastrin Precursors Are Present in Adenomas in the Mouse Polyposis Coli Model - APCmin.**


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The hormone gastrin is now a well recognised growth factor for colorectal adenocarcinomas. The gastrin gene has been shown to be activated in colorectal tumour cells, and precancerous adenomas have been identified. The precursor glycine-extended gastrin-17 (gly-G17) has been shown to have a proliferative effect, and it has been postulated that it acts via an autocrine growth loop. The mouse model of polyposis coli, APC1638N, which contains a stable mutant APC gene leads to the spontaneous production of intestinal and extraintestinal tumours, similar to the phenotype seen in human familial adenomatous polyposis. The aim of this study was to evaluate the role of gastrin precursors in the adenoma-carcinoma sequence.

**Methods:** In this study mice were fed a high fat Western style diet. At termination the mice were examined and samples were taken from normal colonic mucosa and neoplasms which ranged from adenomas with moderate dysplasia to carcinoma-in-situ. Specimens were formalin-fixed, paraffin sections made and stained with polyclonal antibodies directed against progastrin, gly-G17 and amidated G17. Binding of the primary was detected using the avidin-biotin complex technique. The samples were assessed for size and degree of staining.

**Results:** Progastrin was present in all the neoplastic samples and 7/8 normal mucosa. The intensity of staining of progastrin was greater in the neoplastic samples than in normal samples. In addition, in normal mucosa progastrin was confined to the cytoplasm of epithelial cells compared to widespread cytoplasmic staining, together with granular luminal edge staining, indicative of secretion. Gly-G17 was present in 9/10 neoplastic samples in the cytoplasm and stroma but was absent in normal mucosa. No mature amidated gastrin was found in any sample.

**Conclusions:** There was evidence of over expression and secretion of progastrin and de novo expression and secretion of gly-G17 in neoplastic tissue from adenomas to carcinoma-in-situ. This indicates that progastrin/gly-G17 mediated autocrine pathways may be early events in the adenoma-carcinoma sequence. Furthermore this model may be useful in assessing the efficacy of novel anti-gastrin therapies such as the immunogen, Gastrimmune in pre-malignant conditions.

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