Liver T80-T88

MRNA FOR TISSUE INHIBITOR OF METALLOPROTEINASE-1 (TIMP-1) IS EXPRESSED IN ACUTE AND CHRONIC LIVER DISEASE

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Tissue inhibitor of metalloproteinase-1 (TIMP-1) is a potent enzyme inhibitor with activity against the matrix metalloproteinases including interstitial collagenase, which degrades the abnormal collagens that characterise hepatic fibrosis. We have recently described TIMP-1 release by activated hepatic lipocytes cultured on plastic. To determine the relevance of this finding in liver disease we have used a ribonuclease protection assay to detect TIMP-1 expression in acute and chronic human liver disease.

Total RNA was prepared from snap frozen samples of liver by homogenisation in GIT followed by phenol/CCI₂₄ extraction. 20 µg aliquots of RNA were hybridised overnight with an antisense riboprobe to TIMP-1 labelled with ³²P UTP by in vitro transcription. A second RNA sample was hybridised with an antisense riboprobe for S14, a ribosomal protein, expression of which does not alter in disease states. After RNAase digestion, protected hybrids were precipitated, purified and run on an RNA denaturing gel, with visualisation of results by autoradiography. Densitometry readings of the major protected RNA fragment for TIMP-1 were expressed as a ratio relative to the density of the S14 (control) protected fragment.

Normal donor liver (n=4) had a TIMP-1:S14 ratio of 0.86 ± 0.18 (mean ± SD). TIMP-1 is expressed at levels above normal in all chronic disorders studied including: PBC (n=6) 1.26 ± 0.31 (0.05<P<0.01), chronic active hepatitis (n=5) 1.03 ± 0.24 and PSC (n=5) 0.96 ± 0.2. TIMP-1 expression was also dramatically increased in paracetamol-induced hepatic failure (n=3) 1.88 ± 0.6 (0.05<P<0.01). These data demonstrate TIMP-1 expression in both acute and chronic liver injury. We suggest that in chronic liver disease this may contribute to the pathogenesis of liver fibrosis.

Liver T81-T82

SERUM PROCOLLAGEN III PROPEPTIDE LEVELS AND THE PGA INDEX IN THE ASSESSMENT OF HEPATIC FIBROSIS IN ALCOHOLIC LIVER DISEASE, PRIMARY BILLIARY CIRRHOSIS AND VIRAL HEPATITIS.


Persistent elevation of the serum levels of the aminoterminal type III procollagen propeptide (PIIIP) correlate with the activity of hepatic fibrosis. A simple biological index of fibrosis, the PGA index, combines prothrombin time (P) with serum-γ-glutamyl transpeptidase (G) and apolipoprotein A1 (levels (A), since these fall with progressive fibrosis.

SUBJECTS: The two tests were compared in different histological forms of alcoholic liver disease (n=104), primary biliary cirrhosis (n=38), chronic B virus hepatitis (n=27), and healthy age-matched controls (n=30). The ability to correctly identify cases with fibrosis or cirrhosis was determined using receiver operating curves.

RESULTS: For alcoholic liver disease PIIIP and PGA were markedly raised for all histological groups (p<0.0001). PIIIP was especially raised with both alcoholic hepatitis and cirrhosis. For detecting cirrhosis the PGA was 79% sensitive and 89% specific, the PIIIP 85% sensitive and 90% specific. The two tests combined were 71% sensitive but 97% specific.

For primary biliary cirrhosis, both the PGA index and the PIIIP values correlated well with the severity of the disease as determined by the Mayo score (R=0.71 and 0.66 respectively p<0.0001 for both). The combined tests were again 97% specific for the detection of fibrosis.

For chronic B virus hepatitis the levels of both PGA and PIIIP were raised compared to controls (p<0.0001 for all groups).

CONCLUSIONS: Greatly elevated PIIIP levels may detect the sub-group of alcoholics with both hepatitis and cirrhosis. The combined tests may be useful for targeting patients with antifibrotic drugs, and to reduce the need for liver biopsy.

INTERSTITIAL COLLAGENASE EXPRESSION IN CULTURED HUMAN HEPATIC LIPOCYTES AND DISEASED HUMAN LIVER

Department of Medicine, Southampton General Hospital

Hepatic fibrosis is characterized by replacement of the normal hepatic matrix with interstitial collagens. Activated hepatic lipocytes are suspected to be a major source of interstitial collagenase (IC) which can be demonstrated in liver homogenate after acute injury. However methodological difficulties have prevented the definitive identification of its source. We have used molecular and immunological techniques to determine IC expression by human hepatic lipocytes and in diseased human liver.

Lipocytes were prepared from wedges of unused normal donor liver by pronase/collagenase digestion, followed by density gradient centrifugation over arabinogalactan, and cultured on plastic in the presence of 10% FCS. By Northern analysis using a specific cDNA probe, mRNA for IC could be detected in lipocyte RNA after 4 days in primary culture. By dual immunostaining, IC was immunolocalised to the perinuclear cytoplasm of desmin positive KPl negative cells i.e. culture activated lipocytes. Total RNA was prepared from snap frozen samples of liver by homogenisation in GIT followed by phenol/CCI₂₄ extraction. 20µg aliquots of RNA were hybridised overnight with an antisense probe to IC labelled with ³²P UTP by in vitro transcription. After RNAase digestion, protected hybrids were precipitated, purified and run on an RNA denaturing gel. mRNA for IC was only detected in 2 out of 4 samples of normal donor liver but was undetectable in PBC (n=6), PSC (n=5) and chronic active hepatitis (n=5).

These data indicate that activated hepatic lipocytes express IC, but mRNA for IC is undetectable in advanced liver disease. Reduction in IC expression may be a major factor promoting fibrosis in liver disease.
SOLUBLE ADHESION MOLECULES IN IMMUNE LIVER DISEASE.
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Immunohistochemical studies in liver biopsies have shown that several vascular adhesion molecules are induced in a variety of liver diseases, eg. transplant rejection, viral, alcoholic and autoimmune hepatitis. Recently soluble forms of these molecules have been described but their diagnostic and prognostic importance have yet to be defined.

METHODS. Enzyme linked immunosorbent techniques were used to measure soluble ICAM-1, E-selectin and GMP-140 (P-selectin) in serum of patients with autoimmune chronic active hepatitis (AI-CAH), n=6; and hepatitis C related liver disease (HCV, n=7).

RESULTS. Increased levels of soluble ICAM-1 were found in all patients with AI-CAH (233.5 + 263.4 ng/ml, mean + SD) and patients with HCV infection (845.6 + 240 ng/ml). The levels of soluble E-selectin were slightly increased in 50% of patients with AI-CAH and HCV. Similarly, the levels of soluble P-selectin were increased in 50% of patients with AI-CAH and HCV. In patients with active AI-CAH the levels of soluble ICAM-1 and E-selectin fell with subsequent steroid therapy. Levels of soluble ICAM-1 correlated with serum ALT and the levels of E-selectin correlated with P-selectin (p<0.01), no other correlations were noted.

CONCLUSIONS. We have found increased levels of ICAM-1, E-selectin and P-selectin in patients with AI-CAH and HCV related liver disease. The increased levels in active AI-CAH fall with steroid therapy.

DO BILE ACIDS AFFECT STRUCTURE AND FUNCTION OF HUMAN HEPATOCYTE MITOCHONDRIA?
AG Lim, HA Ahmed, RP Jazrawi and TC Northfield, Dept. of Medicine, St. George’s Hospital, London, UK.

It has been suggested that liver damage in primary biliary cirrhosis (PBC) is due to retention of toxic hydrophobic bile acids (eg. chenodeoxycholic acid, CDCA) and that the therapeutic effect of the hydrophilic acid ursodeoxycholic acid (UDCA) is that it reduces this damage; but the mechanism involved in liver damage and the production of anti mitochondrial antibodies have not been defined. Our aim in this study was to examine the effect of hydrophobic and hydrophilic bile acids on structure and function of human hepatocyte mitochondria. Mitochondria were prepared using sucrose gradient ultracentrifugation from wedge liver biopsies obtained from patients without liver disease. To investigate structural effect, we measured mitochondrial protein solubilisation by CDCA and UDCA (0-10 mM). To investigate functional effect, we studied mitochondrial electron transfer by measuring the activity of succinate cytochrome C reductase. Protein solubilisation by CDCA was detected at 0.5 mM bile acid concentration and reached a maximum of 50%; with UDCA it was detected at 2 mM and reached a maximum of only 20%. CDCA markedly inhibited mitochondrial electron transfer by comparison to UDCA for all given bile acid concentrations. At 1 mM bile acid concentration, CDCA achieved an inhibition of 80%, whereas UDCA only achieved a maximal inhibition of 30% at a concentration of 10 mM. A combination of CDCA plus UDCA (up to 0.5 mM of each) gave the same effect as UDCA alone (hepatoprotective effect). We have demonstrated that hydrophobic bile acids damage hepatocyte mitochondrial structure and function and that addition of UDCA is protective. We speculate that the beneficial effect of UDCA in PBC may be related to the improvement in mitochondrial oxygen utilisation and ATP formation, and that hydrophobic bile acid damage to mitochondria may be related to the formation of antimitochondrial antibodies.

OCTREOTIDE IN THE CONTROL OF POST-INJECTION SCLEROTHERAPY HAEMORRHAGE. S.A. Jenkins, R. Shields, A.N. Kingsnorth, R. Sutton, S. Ellenbogen, Dept. of Surgery, Royal Liverpool, University Hospital, Liverpool, U.K.

Bleeding from oesophageal ulcers, oesophageatitis or from the varices themselves after injection sclerotherapy is occasionally massive and difficult to control. Since our current experience with octreotide suggest that it is a safe and effective treatment for the control of the acute variceal bleed, we have examined its efficacy in these post-sclerotherapy problems.

Seventy-seven patients experienced a significant gastrointestinal bleed (blood pressure < 100mm Hg, pulse > 100 b.p.m. or the need to transfuse 2 or more units of blood to restore the haemoglobin levels). The source of bleeding was varices in 42 patients (Child's Group A = 1, B = 9, C = 32), oesophageal ulcers in 31 (Child's A = 3, B = 3, C = 25) and oesophagitis in 4 (Child's A = 2, B = 2). All patients received a continuous intravenous infusion of octreotide (50 μg/h) for between 40 and 140h.

Haemorrhage was successfully controlled by an infusion of octreotide in all patients with oesophagitis, in 30 of 31 patients with oesophageal ulceration and in 38 of 42 patients with bleeding from varices. In the 1 patient with persistent haemorrhage from ulcers and in 2 of the 4 with continued bleeding from varices, haemostasis was achieved by hourly boluses of 50 μg octreotide for 24h. No complications were associated with octreotide administration.

The results of this study clearly indicate that octreotide is a safe and effective treatment for the control of the severe haemorrhage after technically successful injection sclerotherapy.

RANDOMISED TRIAL OF VARICEAL BANDING LIGATION AND INJECTION SCLEROTHERAPY FOR BLEEDING OESOPHAGEAL VARICES. I.K. Ramage, A.E.S. Gimson, M. Panos, K. Hayllar, P. Harrison, D. Westaby, Roger Williams, Institute of Liver Studies, King’s College Hospital, London SE5 9SR, and *Dept of Gastroenterology, Charing Cross Hospital, London W6 8RF.

Injection sclerotherapy is of proven benefit in the management of active variceal bleeding although there remains a significant complication rate and early rebleeding is common. Endoscopic variceal banding ligation is a simple technique that has been suggested to be safer and more effective. The aim of this study was to compare injection sclerotherapy (IS) with banding ligation (BL) in a randomised controlled trial of 103 patients (53 banding and 49 injection sclerotherapy). Active bleeding was present in 38% of the banding group and 47% of the sclerotherapy group. The two groups were similar in terms of age, sex, aetiology, and Pugh score (7.2±0.4 BL vs 8.2±0.3 IS).

Bleeding was controlled in 90% (BL) and 92% (IS) of the patients with active haemorrhage but banding achieved obliteration quicker than sclerotherapy: 39±0.6 days (BL) vs 72±10 days (IS), p<0.004, and 3.4±0.3 endoscopy sessions (BL) vs 4.9±0.5 endoscopy sessions (IS), p<0.006 (mean±SEM). Rebleeding was less common after banding ligation (30%) than after sclerotherapy (53%), p<0.05. There was no difference in numbers of patients currently surviving in the trial in the two groups, BL 52% vs IS 57%, and the Cox proportional hazards regression model showed survival to be related only to Pugh score (p<0.0001). However, fewer patients were censored for liver transplant following banding (1) than following sclerotherapy (7), p<0.05. Ulceration rates were similar in the two groups; perforation occurred in 1 patient (IS); aspiration pneumonia occurred in 2 patients, (both IS).

Variceal banding ligation is a safe and effective treatment which obliterates varices quicker and with a lower rebleeding rate than sclerotherapy.
THE EFFECTS OF INJECTION SCLEROTHERAPY ON GASTRIC EMPTYING IN PATIENTS WITH PORTAL HYPERTENSIVE GASTROPATHY.

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Although injection sclerotherapy has been reported to exacerbate portal hypertensive gastropathy (PHG), the precise mechanisms involved are unknown. One possible explanation is that extravasation of sclerosant into the mediastinum may result in vagal damage thereby altering the rate of gastric emptying (GE) and prolonging the exposure of the already susceptible mucosa to the deleterious effects of acid and pepsin. The aim of this study was to investigate this hypothesis in patients with PHG who had received varying amounts of sclerosant (ethanolamine olate) to obliterate their varices. GE was determined in 28 patients with PHG after an overnight fast. In brief, patients lay semi-recumbent on a large field of view gamma camera and were fed a standard meal of \( ^{99m}Tc \)-labelled bran in porridge followed by a cheese sandwich. Data were acquired at a rate of 1 frame per minute for 90 minutes. After realignment of the images regions of interest were drawn over the stomach and a background-correlated GE curve obtained from which the area under the curve was determined. The pattern of GE was variable, patients displaying either a nonexponential or double exponential pattern. There was no relationship between the volume of sclerosant administered and the observed pattern of GE. However, GE assessed by calculating the area of curve increased with increasing amounts of sclerosant administered to the patients. These results suggest that injection sclerotherapy results in progressive vagal damage which alters GE and may exacerbate PHG.

LONG TERM FOLLOW-UP OF PATIENTS RANDOMISED TO INJECTION SCLEROTHERAPY OR OESOPHAGEAL STAPLE TRANSECTION AS EMERGENCY TREATMENT OF VARICEAL BLEEDING

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We have previously shown that endoscopic sclerotherapy and staple transection of the oesophagus are equally effective in the emergency management of variceal bleeding. Oesophageal varices frequently rebleed for up to 2 years following staple transection which should reduce the risk of rebleeding from this source. We report long term follow-up on 57 cirrhotic patients randomised to injection sclerotherapy (27) or staple transection for the emergency control of variceal bleeding for longer than 42 days. Four patients did not receive the assigned treatment (3 in the surgical group) but results are presented on an intention to treat basis. There were 12 deaths in the sclerotherapy and 15 in the transection group and no significant differences in time to death or cause of death. Rebleeding occurred in 23/27 sclerotherapy and in 24/30 transection patients. The sources of bleeding differed: predominantly oesophageal varices in the sclerotherapy group and ulceration of the oesophageal staple line in the transection group. Blood transfusion requirements were greater in the sclerotherapy group but this difference did not reach statistical significance. We conclude that recurrent upper gastrointestinal bleeding is equally frequent after emergency staple transection or injection sclerotherapy but the most frequent source of bleeding is staple line ulceration in the former and oesophageal varices in the latter.

PLATELET HYPERAGGREGABILITY IN VITRO AND IN VIVO IN INFANALMATIONary BOWEL DISEASE (IBD).

CE Collins, NR Cahill, D Snydercombe-Court, DS Buxton, GI Science Research Unit and Dept of Haematology, Royal London Hospital, London.

Active IBD is associated with thrombocytosis and a thrombotic tendency. Multifocal intestinal microinfarction and a procoagulant state have recently been proposed as contributing factors in Crohn's disease (CD). We have tested the hypothesis that abnormal platelet aggregation contributes to the inflammatory process in IBD. METHODS: i) Platelet aggregation was assessed by the Born method in platelet rich plasma (PRP), from patients with IBD and healthy controls. Thresholds for aggregation to increasing concentrations of arachidonic acid (AA) and time taken for 50% response to AA (250 ug/ml), were measured in PRP containing 200 x 10^6 platelets / ml. ii) Evidence of circulating platelet aggregates in vivo was sought using a modified Wu & Hoak method, in which platelet aggregate ratios are obtained by counting platelet counts in formalin/concentrated EDTA with concentrated EDTA alone. iii) Aggregate formation was also assessed by transmission electron microscopy (EM). iv) IBD activity was defined according to modified Harvey-Bradshaw index. RESULTS: Thresholds for AA-induced aggregation and for response to 250 ug/ml AA, are shown as medians (10th-90th centile for thresholds, IQR for aggregation).AA threshold (ug/ml) 1s (seconds)

| controls | 14 | 250 (125-350) | 109 (67-135) |
| active CD | 15 | 125 (62-250)* | 52 (42-69)** |
| inactive CD | 5 | 125 (250-125)* | 128 |
| active UC | 8 | 250 (81-250) | 70 (56-83) |
| inactive UC | 7 | 250 (81-550) | 100 (50-110) |

*p=0.002, t=0.02, *p=0.009 vs control, *t=0.018 vs inactive CD. Platelet aggregate ratios were determined in active CD (0.958 (0.932-1.009) 24, median (IQR)) n=0.03) and active UC (0.959 (0.824-0.976) 15, p=0.05) than controls (0.984 (0.972-1.013) 14, inactive CD (0.960 (0.970-1.007) 15) or UC (0.980 (0.960-1.020) 18). Microaggregate formation demonstrated by EM was more evident in active IBD than in controls.

CONCLUSION: Increased platelet aggregability in vitro and circulating platelet aggregates in vivo, are associated with active IBD, particularly CD, and may contribute to its pathogenesis.
Microalbuminuria is also considered to be a non-specific marker for acute illness (including myocardial infarction) when it may be an indicator of the acute phase response, and for malignancy when it probably reflects a microvascular response to tumor-related mediators. Microalbuminuria may have a prognostic value in acute illness or response to treatment.

Microalbuminuria has not been previously described in patients with inflammatory bowel disease. We studied microalbuminuria in 70 patients with inflammatory bowel disease (IBD) [ulcerative colitis (n=49), Crohn’s disease (n=21)]. 38 patients were in complete clinical remission and 32 patients had active disease. Microalbuminuria was detected in all patients with chronic inflammatory bowel disease including 10 patients who were not receiving any medication, (212 +/- 234 vs controls mean 26 +/- 13 mg/24hrs, x +/- SD, p < 0.007). Patients with active IBD had higher levels of microalbuminuria compared to patients in remission (mean 298 +/- 179 vs 94 +/- 82 mg/24hrs, p < 0.001). Five patients with active IBD were than sequentially followed up with measurements of microalbuminuria; significantly lower levels were detected when the disease was inactive (active IBD mean 276 +/- 181 vs inactive IBD mean 92 +/- 56, p < 0.03). We also have measured serum Interleukin-6 and Amyloid-A (SAA) as indicators of the acute phase response in the same patients. Statistically significant high levels of SAA were recorded in patients with IBD (111 +/- 177 vs controls mean 11 +/- 9/ul, p < 0.05). SAA was significantly increased in active disease as compared to inactive disease (151 +/- 204 vs 33 +/- 27 ul/ml, p < 0.03). Interleukin 6 levels were detectable in 17 patients with IBD but did not correlate with disease activity. However microalbuminuria correlates more closely with active disease than serum Interleukin-6 and SAA. There was no correlation between levels of SAA and microalbuminuria.

CONCLUSION: Microalbuminuria is present in abnormal amounts in all patients with active inflammatory bowel disease and levels fall when the disease is inactive. Microalbuminuria is probably a consequence of an acute phase response and provides a simple, rapid and cheap test which may potentially be used to monitor the inflammatory bowel disease activity and response to therapy.

**T94**

**TFN INDUCES LEUKOTRIENE B4 PRODUCTION IN AN EPITHELIAL CELL LINE**

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Leukotriene B4 (LTB4) and TFN are potent mediators of inflammation, raised in the mucosa of patients with Inflammatory Bowel Disease (IBD). The origin of LTB4 in this condition is unknown, though neutrophils have been implicated. Recent reports have shown that CaCo2 cells are capable of secreting LTB4 in response to an ionophore. The aim of this study was to determine whether the epithelial cell line HT29 synthesized LTB4 and whether this could be induced by TFN. HT29 (cl.19A) cells were grown to confluence in 6 well plates using a medium containing DMEM, fetal calf serum:10%, Non-essential amino acids:1% and ciprofloxin. Four days following confluence cells were exposed to TFN (100nM), or, the ionophore A23187 (1mM). Supernatants were saved at 0,10 and 20 minutes. Following extraction on C2 columns (methylene,water,ethanol,hexane,methanol/formate) LTB4 was determined by ELISA (Amersham). Neutrophils and biopsy samples from patients with IBD served as positive controls.

Both TFN and A23187 induced LTB4 production by HT29 cells. Production per 4x106 cells was 11.62+4.94 pg/t: t0:7.96+1.2pg and t20:19.05+0.4pg (P<0.05). A23187 t0:14.05+0.1pg:t0:11.8+2.6pg and t20:15.4+3.0pg.

This study suggests that epithelial cells may have a greater role in large bowel inflammation than previously suspected.
WHAT IS THE ABNORMALITY IN POSTCHILDBIRTH/HYSTERECTOMY CONSTIPATION? - A PHARMACOLOGICAL STUDY OF COLORFUL DRUG/NERVE-MEDIATED RESPONSES AND PERISTALIS

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University Department of Surgery, Royal Infirmary, Glasgow & University Department of Pharmacology, Glasgow University

There is a distinct group of female patients who attribute the onset of severe constipation to childbirth or hysterectomy. Strips of sigmoid colon (1.0 x 2 cm) were taken from 8 such patients (n=22) and 11 controls (n=23) and equilibrated in Krebs' solution at 37°C.

Electrically stimulated (ES) produced excitation (cholinergic) Tetrodotoxin (1 x 10^-5 M) sensitive contractions (contraction 32 HZ). In the presence of spontaneous or carbobol induced tone, ES produced Phentolamine (1 x 10^-5 M) and Atropine (1 x 10^-5 M) insensitive relaxations (insensitive 1-8 Hz). Tissues from constipated patients were more sensitive to carbobol than controls p<0.01 (regression analysis of dose response curves). Peristalsis was induced in 10 cm segments of sigmoid colon (Trendelenberg). In controls, increases in intraluminal pressure (5.5 mmHg ± 2, mean ± SD) produced peristalsis which was reduced from a mean frequency of 1.3 ± 0.3 per min to 0.5 ± 0.3 per min by Hexamethonium (1 x 10^-5 M) (p<0.005). The frequency of contraction was increased by Neostigmine and abolished by Procaine. In tissues from constipated patients, a mean rise in intraluminal pressure to 7.5 ± 1.5 mmHg or adding Neostigmine failed to induce peristalsis.

These results show that while both excitatory and inhibitory nerves are present, tissues from constipated patients are more sensitive to cholinergic agonists and less susceptible to afferent stimuli mediating peristalsis than control tissues. This would support the hypothesis that there is an intrinsic colonic autonomic nerve abnormality.

Trendelenberg, P (1917) Arch exp Path Pharm; 81: 55.

TOPICAL APPLICATION OF A NITRIC OXIDE DONOR REDUCES INTERNAL ANAL SPHINCTER TONE: THERAPEUTIC IMPLICATIONS


Nitric Oxide (NO) is one of the major neurotransmitters mediating anorectal relaxation. Its ability to relax the internal anal sphincter may have implications for the treatment of conditions in which high resting pressure was a probable pathogenic role. We have studied the effect of topical glyceryl trinitrate (GTN), an NO donor, on resting anal pressure (a reflection of internal anal sphincter tone).

Maximum resting pressure (MRP) was recorded using a water-filled microballoon system in 15 subjects before and after external application of 0.2% GTN (Pericort). Cusil U.K. diluted 1:10 in yellow soft paraffin to the anus. This dilution was used to avoid severe headaches caused by stronger preparations. Three other subjects were studied as controls using a placebo ointment. The investigator was unaware as to which ointment was being applied.

MRP decreased in all GTN-treated subjects from 1012±35cmH2O (means±d.) to 74±34cmH2O, a mean decrease of 29% (95% c.i.: 20-39%: t=6.62; p<0.0001). Repeated studies, in two subjects showed a persistent decrease 8 hours after application. Two subjects reported mild, transient headaches. There was no change in pressure in the control subjects (Pre: 67±7, Post: 67±8; change: 0±25cmH2O). This differed from the treatment group (t=4.63, d.f.=2, p<0.02).

We conclude that internal anal sphincter tone is significantly reduced following the application of topical GTN. This may have clinical application by reducing the need for surgical treatment of conditions associated with an increased resting anal pressure, such as anal fissure, haemorrhoids and certain types of constipation.

RELATIONSHIP BETWEEN ANAL PRESSURE AND ANODER- MAL BLOODFLOW: THE VASCULAR PATHOGENESIS OF ANAL FISSURE

W.R. Schouten, MD; J.W. Briel, MD, and J.J.A. Alexander, MD (introduced by M. van Blankenstein). University Hospital Dijkzigt, Rotterdam, The Netherlands.

The poor healing rate of anal fissures and their predilection for a posterior midline location have been attributed to insufficient blood supply at the posterior commissure. It has been suggested that the increased activity of the internal anal sphincter further decreases the arterial supply. The aim of this study was to investigate this hypothesis by evaluating the relationship between anal pressure and anodermal bloodflow. In 58 consecutive patients (M/F: 27/31, median age: 50 yrs, range: 18-85) with various anorectal and colonic disorders, maximal anal resting pressure (MARP) was recorded. Simultaneously, Laser Doppler Flowmetry was performed to assess perfusion of the anoderm at the posterior midline using a Periflux PF28 Laser Doppler Flowmeter (Perimed, Sweden). The flowmeter signals represent the flux which is defined as the number of blood cells moving in the measured volume X mean velocity of these cells. We found a significant correlation between MARP and perfusion of the anoderm (r=-.585, P<.001, Spearman). Both measurements were also performed in patients with faecal incontinence (N=6) and anal fissure (N=5). In patients with anal fissure MARP was significantly higher than in patients with faecal incontinence (125±22 vs. 42±18 mm Hg, P<.001, student t-test), whereas the perfusion at the base of the anal fissure was significantly lower (0.42±0.08 vs. 1.52±0.77 W/m2). Our findings strongly support the hypothesis that anal fissures are ischaemic ulcers.
T99

**ANAL ENDOSONOGRAPHY**

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Increased colonic motor activity can cause either diarrhoea or constipation. The mechanisms underlying these responses are ill understood. Oxytocin, the long-acting somatostatin analogue, has been reported to both stimulate and to inhibit motility under different experimental conditions. We hypothesised that oxytocin might inhibit spontaneous high pressure waves in the denervated rabbit distal colon. The specific aims of this study were to establish the basal pattern of motility in isolated perfused rabbit distal colon and then to test the effect of oxytocin on this spontaneous pattern of motility in this model of extrinsically denervated colonic motility. Methods: Oxytocin was administered to New Zealand white rabbits and placed in an isolated organ chamber and perfused with Krebs-Ringers bicarbonate (95% O2/5% CO2) through the IMA. Motility was quantified with six ports containing disposable manometry catheters. A computer program calculated the motility index (MI曼联/米) by integration of the area of the digitized signal (Nsec) and counted high pressure peaks of different magnitudes (<10, 10-20, 20-30, >30 mmHg). Oxytocin was infused intravenously. Significance p<0.05 by ANOVA. Results:

<table>
<thead>
<tr>
<th>% INHIBITION MI</th>
<th>% INHIBITION PEAK PRESSURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin 10-10^{-4} M</td>
<td>20.3% 20.1% 39.5% 39.5%</td>
</tr>
<tr>
<td>3x10^{-5} M</td>
<td>21.2% 21.3%</td>
</tr>
<tr>
<td>10^{-4} M</td>
<td>56.4% 62%</td>
</tr>
<tr>
<td>10^{-3} M</td>
<td>83.5% 63%</td>
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Active spontaneous motor activity developed after isolation of the colon. The basal MI was 458±16.8. Infusion of oxytocin resulted in a concentration dependent drop of MI (EC50 5x10^{-5} M, max inhibition 24% and decrease in peak pressures in the ranges 10-20 and >20 mmHg but not 0-10 mmHg (EC50 3x10^{-5} M, max inhibition of peak waves >20 mmHg 65%). These data indicate that oxytocin decreases the motility index by inhibition of high pressure waves in the rabbit distal colon. It is possible that oxytocin may prove a useful pharmacotherapeutic probe for the amelioration of the postoperative motility perturbations generally characterised as ileus.

T101

**TOTALLY STAPLED RESTORATIVE PROCTOCOLECTOMY - FUNCTIONAL RESULTS OUTWEIGHT PUTATIVE RISKS**

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Restorative proctocolectomy (RP) and endosanal mucosectomy results in a high incidence of night leakage. Totally stapled RP is a relatively simple technique but has a putative tumour risk in the residual anal canal mucosa.

Fifty-one consecutive patients undergoing totally stapled RP were functionally assessed. All but 3 had a temporary loop ileostomy. There were no operative deaths. Anastomotic leakage occurred in 4 patients. The median duration of surgery was 215 mins (range 150-375); blood loss was 345 ml (50-1300); blood transfusion was 0 units (0-3) and hospital stay was 12 days (8-50).

At a median followup of 12 months (6-48) the median daily and nocturnal stool frequencies were 4 (3-12) and 0 (0-6) respectively. Four patients had the pouch removed (2 Crohn's pouchitis, 1 ischaemic pouch and 1 pelvic sepsis). Only 2 patients had episodes of nocturnal incontinence. A further 3 patients had leakage by day. All but 2 patients had resumed normal daily activities.

These data suggest that a totally stapled ileoanal pouch gives excellent functional results, particularly with regard to night leakage. This benefit may outweigh the putative neoplastic risk of a retained anal canal mucosa.

T102

**Audit T102-T105**

Audit of long term acid suppressing therapy in General Practice.

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We have previously shown that many patients on long term acid suppressing therapy (>6 months continuous therapy) have no diagnosis established with serious implications for medical practice and drug costs. We therefore audited use of long term acid suppressing treatment in 7 general practices in the Harrow area, (60 148 patients) then set agreed standards for the management of these patients and closed the loop by re-audit after a 6-9 month interval.

Patients were identified from repeat prescribing data. Investigations and diagnoses were then obtained from patients notes. Standards were set by seminars/discussion between two consultant gastroenterologists and the general practitioners involved. The second audit collected data on all initial audit patients and any new patients on treatment for 6 months or longer.

492 patients were taking long term therapy at the time of the initial audit. Applying the agreed criteria 148(30%) fell outside the agreed standards (uninvestigated abdominal pain n=93, duodenal ulcer with diagnosis >5 years before start of long term therapy n=45, others n=10). Audit 2 showed a small fall in total numbers of patients taking long term therapy (to 468) and a decrease in patients falling outside the guide-lines, n=105 (22%) p<0.0006. This decrease was mainly due to a fall in the numbers of patients who had inadequate investigations prior to starting long term therapy with a history of previous duodenal ulceration (n=20, 4%) p=0.01 compared to initial audit. The number of patients with undiagnosed abdominal pain did not show a significant fall (audit 2, n=82 [18%], p=0.8).

Audit can reduce the number of patients treated inappropriately with long term acid suppressing drugs. The effect is however relatively small and the same must be significant doubts as to the cost effectiveness of this intervention unless more patients with "non-ulcer dyspepsia" can have therapy discontinued.
A STUdy of the Inappropriate USE of uPper Gastrointestinal Endoscopy Online M.A. Bell G.D. McKay R.P.
The Royal College of Surgeons, London

The aim of the current study was to assess the accuracy of the gastroenterologists' diagnosis of upper gastrointestinal disease (DCBE).

400 consecutive cases referred to four units within one region were assessed for their inappropriateness by a panel of independent gastroenterologists (n=7) without discussion. The same cases were rated by software incorporating American opinion (the Rand criteria). Only 45 (12%) of the cases were considered inappropriate by the British panel, because of lack of features of ulcer disease and evidence of Irritable Bowel Syndrome (n=15), because of current effective H2 Antagonist treatment (n=9), recent OGD or Barium Studies (n=9), or others (n=17). (Some cases were assigned inappropriate for more than one reason.) However 120 (35%) of all cases assessed by the American Software were found to be inappropriate. These decisions were arrived at for different reasons, because of insufficient treatment (n=77), or resolution of symptoms (n=16), and others (n=27). In the USA it is recommended that 1 month anti-ulcer treatment is tried before considering endoscopy, whereas British clinicians put less emphasis on such a trial. Of the 45 cases found inappropriate by the British doctors, no significant pathology was revealed at endoscopy, whereas out of the 120 cases judged inappropriate by the Rand criteria, 3 OGDs, 2 OGDs and 1 Gastric Cancer were discovered.

Additional work by this group has emphasized why further study is necessary. A second project looked at the variance of opinion across different disciplines on endoscopy use for common scenarios. Differences of opinion were seen both within and between specialties and disciplines. Current literature is inadequate to assist with defining appropriate use. This study has attempted a quantitative assessment of inappropriate use and serves to encourage further work to guide appropriate use.

The wound complication rate has improved as a result of operations being performed by senior registrars rather than SHO's. The use of a dedicated theatre has resulted in more appropriate and a higher proportion of patients discharged. Regional and/or local anaesthetic wound infiltration has reduced anaesthetic agent usage resulting in quicker recovery times and reduced side effects following surgery. Pain control has been achieved with oral analgesic regimes tailored to individual procedures. Interventional radiology as a result of audit has led to the provision of a better service with improved patient satisfaction.

Pancreas T106-T112

THE ROLE OF CHOLECYSTITOKININ (CCK) IN THE HORMONAL STIMULATION OF Pancreatic Enzyme Synthesis AND Secretion, J.W.Konturek, A.Gawronska-Bork, R.Bork, and W.Domschke, Department of Medicine, University of Muenster, Germany and Department of Medicine, Medical School of Bialystok, Bialystok, Poland

Activation of type A receptors by CCK or coerulein is known to stimulate pancreatic enzyme secretion but its role in enzyme synthesis remains unclear. In our study we investigated the possibility of a potent CCK-A receptor antagonist, to investigate the role of CCK-A receptors in pancreatic enzyme synthesis and secretion. Five healthy male volunteers were intubated with double-lumen duodenal tube and duodenal aspirates were collected during 30 min basal periods and then during pancreatic stimulation with i.v. infusion of coerulein (50 pmol/kg-h) plus secretin (80 pmol/kg-h) during continuous three 15 min periods. The same procedure was repeated, but secretin-coerulein infusion was combined with a constant dose of 1.20 pmol/kg-h. The volume and outputs of HC03, protein and enzymes (tAmylase, lipase, trypsin, chymotrypsin) in duodenal aspirates and gallbladder volume by sonography were determined at 15 min intervals. Plasma samples were also drawn for total plasma amino acid assay by ninhydrin method to assess the activity of pancreatic enzyme synthesis.

Infusion of coerulein plus secretin increased significantly the volume of aspirate from basal 45±29 to 131±40 ml/30 min, the outputs of HC03 from 0.4±0.2 to 19±4 ml/h, 30 min, protein rose fourfold and enzyme output twofold. During those periods, plasma amino acid level decreased from initial 1.9±0.5 mmol/l to 1.0±0.3 mmol/l (p<0.01) and the gallbladder volume from initially 26±4 to 54±4 ml. Addition of L to the secretin-coerulein infusion, the volume and HC03 in duodenal aspirates were unchanged but the pancreatic protein and enzymes output decreased by about 20%. The total plasma amino acid level remained unchanged after L. Addition of L almost completely prevented the contraction of the gallbladder.

Our results indicate that: (1) Activation of type A CCK receptors is involved in the coerulein-secretin stimulated pancreatic enzyme secretion but does not appear to be involved in the pancreatic protein synthesis; (2) the increase of the pancreatic enzyme secretion correlates with simultaneous decrease of total plasma amino acids.
THE PRACTICAL VALUE OF SERUM INTERLEUKIN-6, POLYMORPHONUCLEAR ELASTASE, C-REACTIVE PROTEIN AND TUMOUR NECROSIS FACTOR AS EARLY PROGNOSTIC MARKERS IN HUMAN ACUTE PANCREATITIS. L. Formella, A.N. Kingsnorth, Department of Surgery, Royal Liverpool University Hospital, Liverpool.

A number of prognostic serum markers are emerging which may have equal or superior sensitivity and specificity to scoring systems in acute pancreatitis (AP). No single study has prospectively evaluated these serum markers viz. interleukin-6 (IL-6), polymorphonuclear elastase (PMNE), C-reactive protein (CRP) and tumour necrosis factor (TNF). The purpose of the present study was to compare the serum markers with the Apache-II disease severity scoring system as early indicators of disease severity, in a single patient cohort.

In 40 patients scored within 24hr of admission, Apache-II > 8 was taken to indicate severe AP (Ref. 1). Serum II-6, PMNE, CRP and TNF were measured daily for 5 days. In patients with mild AP (n = 36) at 24hr IL-6 was 126 ± 68 pg/ml, CRP 59 ± 28 mg/L, TNF 35 ± 13 pg/ml and PMNE 80 ± 24 μg/L. At 48hr IL-6 was 133 ± 51 pg/ml, CRP 70 ± 22 mg/L, TNF 38 ± 11 pg/ml and PMNE 78 ± 13 μg/ml. In patients with severe AP (n = 4) at 24hr IL-6 was 205 ± 64 pg/ml, CRP 51 ± 20 mg/L, TNF 38 ± 13 pg/ml and PMNE 510 ± 40 μg/L. (K.6.4 patients with mild AP (p < 0.001). At 48hr IL-6 was 228 ± 78 pg/ml, CRP 67 ± 18 mg/L, TNF 11 ± 8 pg/ml and PMNE 630 ± 52 μg/L.

Apache-II accurately predicted the 4 patients with severe disease at 48hrs. At 24hr and 48hr the only reliable prognostic marker was PMNE. Thereafter CRP and IL-6 reliably predicted disease severity. PMNE alone equals the sensitivity and specificity of Apache-II scoring. PMNE is a simple, rapid blood test for predicting severity in AP in the first 24hr, and is superior to physiological scoring and other serum markers.

**EXPRESSON OF PS2, A PUTATIVE GROWTH FACTOR, IN NORMAL AND MALIGNANT PANCREAS**

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ps2 is a 60 amino acid secretory polypeptide which is found in the epithelial cells of the normal stomach and duodenum, as well as adjacent to damaged mucosa in the gastrointestinal tract. It is believed to belong to a new family of growth factors which include the structurally similar pancreatic spasmolytic polypeptide which is mitogenic for epithelial cells, including colorectal cell lines. Pancreatic carcinoma remains a tumour with poor prognosis whose growth requirements are poorly understood. The aim of this study was to analyse the expression of ps2 in pancreatic carcinoma and compare it with normal pancreas and chronic pancreatitis. Methods. 5μm sections of formalin-fixed paraffin-embedded material were examined from normal pancreas (n=5), chronic pancreatitis (n=10), ductal adenocarcinoma (n=42) and ampullary carcinoma (n=12). The staining pattern of two antibodies (Ab) to ps2 were compared, (1) a polyclonal Ab (pcAb), pN-R-2, used at a dilution of 1/200 and (2) a commercially available monoclonal antibody (mAb) ps2 (Cis/UK Ltd) diluted 1/120. Immunostaining was performed using immunoperoxidase detection methods with 3,3-diaminobenzidine as the chromogen.

**Results.** Normal pancreas. No immunostaining was observed with either antibody except in one small area of ductular proliferation. Chronic pancreatitis, 8/10 cases stained with both antibodies, immunostaining was focal and confined to the ducts. Adenocarcinoma, 19942 (45%) cases showed immunoreactivity with pCAB. In 30 cases immunostaining was repeated using mAb with 19 positive cases (63%). Comparable cytoplasmic staining was seen with the exception of 4 pcAb negative cases where focal staining was detected with mAb. Ampullary carcinoma. Immunostaining with ps2 was seen in 5/10 (50%) tumours and 8/10 cases using the mAb. Conclusion. Our data shows focal expression of ps2 in pancreatic and ampullary carcinoma in contrast with less marked immunoreactivity in chronic pancreatitis and no expression in normal pancreas. Thus ps2 plays a role in the growth of these highly malignant tumours.


**LAPAROSCOPIC AND LAPAROSCOPIC ULTRASOUND IN THE EVALUATION OF PANCREATIC CARCINOMA**

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The early and accurate staging of pancreatic cancer will allow appropriate institution of both curative and palliative treatment. The value of transcutaneous ultrasonography, computerised tomography and angiography in assessing resectability is recognised although laparoscopy may be useful in detecting peritoneal dissemination of tumour. A 7.5MHz linear array laparoscopic ultrasonic probe (Aloka, KeyMed Ltd) for insertion via a 10mm disposable port has been developed for the evaluation of solid organs at laparoscopy.

Thirty consecutive patients with suspected pancreatic carcinoma were considered on initial investigations to have resectable disease underwent diagnostic laparoscopy (DL) and laparoscopic ultrasound (LapUS). Features identified at DL included hepatic metastases (6 patients), peritoneal spread (2) and malignant ascites (1). LapUS identified further hepatic deposits (5), lymphadenopathy (5), local infiltration (6) and portal vein involvement or occlusion (8).

Overall, DL identified advanced disease in six patients (20%). LapUS detected irresectability in a further six patients (20%). There were doubts regarding resectability in three patients all of whom proved irresectable at surgery. Only two patients thought to have a resectable lesion by this technique were beyond resection at laparotomy. The remaining 13 patients underwent resection.

Laparoscopic ultrasonography has improved staging of pancreatic carcinoma and should be undertaken early in the management of this disease.

**AN ENDOscopic CONGO RED TEST (ECRT) PREDICTS THE PRESENCE AND TOPOGRAPHICAL EXTENT OF GASTRIC ATROPHY.**

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The prevalence of chronic gastritis with atrophy increases with age and ageing is also associated with proximal migration of the fundic-pyloric junction. This transition between non-acid and acid-secreting gastric mucosa can be distinguished using the histochemical and morphological features of gastritis. The aim of this study was to evaluate the relationship between the location of the fundic-pyloric junction, H pylori, gastric atrophy, acid output and age, and to assess the ability of dye staining to identify atrophy, 50 healthy males (age 18-87y) were prospectively studied with an ECRT. At endoscopy the gastric mucosa was finely sprayed with Smolded Congo Red in 0.5% HCO3. After 1-2min, the distance from the pylorus to the red-black colour junction was measured in four quadrants, (greater and lesser curves, anterior and posterior walls) with a calibrated catheter, the sum of these being the CR score. Gastric atrophy and H pylori status (culture, urease test, histology) were assessed in antral, body and fundal biopsies. Basal, sham-fed and maximal acid outputs (BAO, SAO, MAO) were determined on a separate day.

Subjects with gastric atrophy (12/50, mean age 76.3±1.9y) had greater mean CR score (59 vs 24cm, p<0.001) than those without atrophy (38/50, mean age 42.8±2.7y). CR score correlated with the extent of atrophy (antral 32; body 44; pyloric 101cm, p=0.04). A CR score >34cm was predictive of atrophy (positive predictive value 75%, negative predictive value 92%) while a CR score <27cm accurately excluded atrophy (negative predictive value 96%). The CR score correlated with age (r=0.43, p<0.01) and was inversely correlated with acid secretion (BAO r=-0.34, p<0.01; SAO r=-0.45, p<0.002; MAO r=-0.58, p<0.001). Atrophy was strongly associated with H pylori: 10/12 subjects with atrophy had H pylori; 2/13 H pylori negative subjects had atrophy (p<0.001).

Thus, the ECRT identifies gastric atrophy at endoscopy and is a guide to its topographical extent. It confirms that proximal migration of the fundic-pyloric junction with age is associated with decreased acid secretion and is due to H pylori associated gastric atrophy.
T115

ENDOSCOPIC INJECTION THERAPY FOR BLEEDING PEPTIC ULCER; SCLEROSANTS ARE UNNECESSARY. C.E. CHoudaki, K.R. Palmer, GI Unit, Western General Hospital, Edinburgh

The prognosis of patients presenting with severe, acute peptic ulcer haemorrhage is improved by endoscopic injection therapy, but the optimum technique is controversial. Indeed sclerosants may be harmful because they cause mucosal damage. 107 consecutive patients presenting with major peptic ulcer haemorrhage were randomised to endoscopic injection with 3-10 ml of 1:100,000 epinephrine (Group 1, 55 patients) or to combination therapy of epinephrine and 0.5-3.0 ml of 5% ethanolamine (Group 2, 52 patients). Seven patients were excluded because the bleeding point was not identified or initial haemostasis could not be achieved by epinephrine. All patients were actively bleeding or had a non-bleeding protruberant vessel at the time of endoscopy. Endoscopic injection was undertaken by a single endoscopist; admitting surgeons and physicians were unaware of randomisation details.

The two groups were well matched with regard to age, shock, haemoglobin concentration, endoscopic findings, other medical diseases, and NSAID use. Active bleeding occurred in 8 group 1 patients (14.5%) and 7 group 2 patients (13.5%). Operation rates (7.5% in both groups), median transfusion need (4.0 and 4.2 units), and mean hospital stay (7 and 6 days) were similar in both groups. No acute complications occurred and only one patient died from myocardial infarction 8 days after injection.

In patients presenting with major acute peptic ulcer haemorrhage, the addition of a sclerosant confers no advantage over injection therapy with epinephrine alone.

T116

DIAGNOSTIC, THERAPEUTIC AND PRACTICAL ADVANTAGES OF SMALL BOWEL EXAMINATION WITH A PUSH TYPE ENTEROSCOPE


The small bowel beyond the proximal duodenum may be assessed by two endoscopic techniques: balloon-driven (Sonde)-type and push-type enteroscopy. The latter, although unable to visualise the entire small bowel, is quick, and has standard angiography controls and channels, allowing intestinal and biopsy procedures. This study describes experience with the Olympus SIF 10 push-type enteroscope.

Results: During a 12 month period, small bowel examination was specifically indicated in 46 cases. Procedures were well-tolerated under standard benzodiazepine sedation. Mean insertion was 55 cm (range 25-90 cm) from the pylorus- in some cases assisted by guide wire or an experimental duodeno-lateral overture. Mean procedure duration was 15 min (5-35). The most frequent indications were: obscure anaemia (n = 15) (a diagnosis was achieved in over one third); abdominal pain and/or vomiting (n = 9); feeding problems (15%). In 33% cases, diagnoses were made which could not have been achieved by standard upper GI endoscopy- in the distal duodenum: bleeding ileomyoma (n =1) and secondary melanoma deposit (1), and the jejunum: adenocarcinoma (1); strictures due to enteritis follicularis (1) or to unknown cause (2); Kapossi's sarcoma (1); ulceration due to severe coeliac disease (1); angiodysplasia (2); radiation enteritis (1); NSAID-induced mucosal damage (1); and jejunal giardiasis (3). Therapeutic options were used in 33% cases, and included: TTS balloon stricture dilatation (n =4) NAD-LA laser (2) and bipolar electrocoagulation (2) treatment of bleeding lesions; placement of feeding tube in dilated jejunum (3); direct jejunostomy tube (2); stiching of nasojugal feeding tube to oesophagus to prevent recurrent displacement by vomiting (1); placement of stent in obstructing jejunal polyp (1). Of the 46 patients studied, 30 had some form of recurrent bleeding; 22 had the instrument repeated (n = 11), all with the same instrument. In the remaining 14 cases, a new instrument was used. Of these 14, recurrent bleeding in 10, recurrent blood loss in 2, and successful colectomy in 2. The instrument has not yet been used for sclerotherapy.

Conclusions: Push-type enteroscopy is an extremely practical, and cost- and time-effective. It has provided small intestinal diagnoses and treatments not possible by other endoscopic techniques.

T117

LOCAL EXCISION OF MALIGNANT COLORECTAL POLYPS

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This study reviews the results and 5 year follow up of patients who underwent local endoscopic resection of malignant polyps at St Mark's between 1973 and 1987. One hundred and twelve malignant polyps were resected from 111 patients (59 female, 52 male, mean age 63 yrs. range 24-87yrs).

Site of Polyp No. Size mm. No. 
Rectum 13 (11.6%) <10 6 (5.4%) 
Sigmoid 21 (19.2%) 10-15 13 (10.7%) 16-20 5 (4.3%) Descending 18 (15.5%) 20-29 8 (6.7%) 30-35 2 (1.6%) Ascending 2 (1.8%) 40-49 0 Caecum 1 (0.9%) >50 1 (0.8%) 

Histology of Polyp No. Differentiation
Ca in Tubular Ad. 27 (24.1%) well. 59 (52.7%) 
Ca in Villous Ad. 13 (11.6%) mod. 50 (44.6%) 
Ca in Tubulovillous Ad 43 (38.4%) poor. 3 (2.7%) 
Polypos Ca 29 (25.9%) 

Histological examination showed excision to be complete in 82 patients (73.5%), incomplete or doubtful in 29 (26.5%). Of the patients whose polyps were completely excised 81 received no further treatment (64 were alive and well at 5yrs, 18 had died of unrelated causes and 3 died of carcinomatosis of unknown origin), and 1 patient who had multiple polyps underwent elective colectomy and was alive with no recurrence at 4 years. Of the 29 patients with incompletely excised polyps 15 received no further treatment (14 showed no sign of recurrence at 5 yrs and 1 patient died from carcinomatosis following local recurrence) and 14 underwent surgical resection. Histological examination of 28 resected specimens showed 11 patients had no evidence of remaining tumour, 1 had a Dukes B and 2 patients Dukes C tumours. All remained well at 5 yrs. In the 4 cases of recurrent invasive cancer, the original polyps were sessile or broad-based, 2 requiring piecemeal polypectomy: local excision was shown to be incomplete in all 2 poorly differentiated, 1 mod. diff. 1 well diff.

We conclude from this study that local excision alone is safe and effective treatment for most endoscopically resectable malignant polyps. Surgery should be considered when the resection margin is incomplete particularly if the tumour is of a high grade of malignancy.

T118

IMMUNOLOGY T118-T122

PBC SPECIFIC M2 AUTOANTIBODIES IN PATIENTS WITH RECURRENT URINARY TRACT INFECTION USING AN ELISA AND PURIFIED PYRUVATE DEHYDROGENASE. Butler P., Hamilton-Jiller J.†, Baum H., Burroughs A.K. "Hepatology & Liver Transplantation, Department of Microbiology, Royal Free Hospital, Hampstead, London NW3. "Division of Life Sciences, Kings College, Campen Hill Road, London W8".

We have shown using SDS-PAGE of beef heart mitochondria and western blotting, low titre anti-mitochondrial antibodies (AMA) in patients with a history of recurrent urinary tract infection (UTI) but no evidence of liver disease. The most common reaction was against E2 alone (in 52% of patients), the 74 kD component of pyruvate dehydrogenase (PDH) - the major autoantigen of PBC. The results have been questioned as being due to non-specific binding or naturally occurring mitochondrial antibodies (NOMA). Thus, using an ELISA based on purified PDH we detected and quantified anti-PDH antibodies in 4 study groups: normal controls (n=38), PBC's selected for anti-T4 kD positivity (n=48), chronic liver disease (CLD) controls (n=30), recurrent UTI's (n=43). Values >2 SD above the mean for normal controls were considered positive. ELISA was positive in all of the PBC patients (100%), 1 of the normal controls (4%), 5 CLD patients (17%) and 23 recurrent UTI patients (54%)- p <0.002 for recurrent UTI group versus controls and p <0.05 chronic liver disease. This confirmation of true AMA reactivity in recurrent UTI patients with no apparent liver disease makes that there is non-specific binding of antibodies on western blots and that reactivity it is not due to NOMA's. Importantly, CLD patients who are known to have a high prevalence of antibodies to gram negative bacteria had a much lower incidence of anti-PDH antibodies compared to the recurrent UTI group, in previous bacteremias this common in CLD patients does not explain our finding. We conclude that not only the nature of the organism but also the route of infection may explain the pathogenesis of M2 specific antibodies and provides a basis for antimicrobial mimicry in PBC.
T119

EFFECTS OF INTERFERON-\gamma AND TUMOUR NECROSIS FACTOR-\alpha ON IFN-\gamma EXPRESSION ON GASTRIC MUCOSAL BIOPSY CELLS CULTURED IN VITRO. R.P. Sturgess, M. Kontikou, J. Spencer*, L.B. Hooper, M.W. Makgoba, P.J. Cillitira. St Thomas' Hospital and University College and Middlesex Hospital School of Medicine*, London.

Leucocyte adhesion is a crucial step in the development of inflammatory responses. Interleukin-1 (IL-1) mediates a variety of immunological and cell interactions, including MHC-restricted presentation, by binding to the leucocyte adhesion receptor molecule LFA-1. Intestinal inflammation induces increased expression of ICAM-1 within the intestinal lamina propria as detected by immunohistological techniques. Unlike non-intestinal inflammation, however, ICAM-1 is not induced in the epithelial cell compartment, but on the immediately adjacent lamina propria cells. In contrast, adenocarcinoma-derived intestinal cell lines express ICAM-1, which can be increased by the addition of cytokines to the culture medium. The potential role of intestinal epithelial cells as antigen presenting cells makes ICAM-1 expression by intestinal epithelial cells, and its modulation by cytokines, of importance. We have studied the effect of interferon-\gamma (IFN-\gamma) and tumour necrosis factor-\alpha (TNF-\alpha) on ICAM-1 expression in human jejunal mucosal biopsies cultured in vitro, to explore further its role in the immunopathogenesis of gastrointestinal disease.

Patients (n=8) subsequently shown to have normal histology, underwent small intestinal biopsy for diagnostic purposes. The expression of ICAM-1 was investigated by immunohistochemistry on biopsies that had been cultured for 24hrs with (FN-\alpha or TNF-\alpha or both at concentrations of 10, 100 and 1000U/ml). Biopsies cultured with medium alone or 10mg/ml of phytahemagglutinin (PHA) served as negative and positive controls respectively.

Expression of ICAM-1 on the lamina propria cells was increased following culture with IFN-\gamma in 7/8 patients, with TNF-\alpha in 5/8 patients and with both IFN-\gamma and TNF-\alpha in 5/8 patients. Culture with PHA induced marked increases in ICAM-1 expression on the lamina propria cells but not on the adjacent epithelium. There was no expression of ICAM-1 on the epithelium of any of the biopsies before or after culture with the cytokines.

We have demonstrated that ICAM-1 expression can be upregulated on the lamina propria cells, but not the epithelium, of human jejunal biopsies cultured in vitro, a model that more closely resembles the in vivo situation, in the presence of IFN-\gamma and TNF-\alpha. This study supports the hypothesis that the superficial lamina propria is a major site of immune activation in the intestinal mucosa.

T120

DECREASED LAMINA PROPRIA LYMPHOCYTE RESPONSES TO H. PYLORI IN PATIENTS WITH GASTRIC H. PYLORI COLONIZATION. S.J. Pan, A. Chua, C.N. Shahi, C. O'Farrelly, P.F. Wain, K.J. Kelleher. Dept of Gastroenterology and Clinical Medicine, St James' Hospital and Trinity College Dublin, Ireland.

Helicobacter pylori (H. pylori) is a spiral organism that colonises human gastric epithelium. The aim of this study was to evaluate the cellular immune response of gastric lymphocytes to H. pylori antigens in individual positive and negative for H. pylori colonization. We measured the in vitro proliferative response of lamina propria lymphocytes (LPLs) isolated from gastric mucosa to inactivated whole cell H. pylori antigens, phyhaemagglutinin (PHA) and anti-CD3 (OKT3) in 28 dyspeptic patients undergoing upper gastrointestinal endoscopy. In addition, IFN-\gamma production by LPLs was measured. LPLs were co-cultured with irradiated (2500 rad) autologous PBMCs as accessory cells.

LPLs proliferative response to H. pylori were significantly reduced in H. pylori positive individuals (400±448 vs 3032±418, X±5E.M. 3H-TdR, cpm, P<0.02)However there were no significant differences seen between the two groups in their responses to PHA and OKT3 (771±613 vs 775±51564, 6104±493 vs 6213±821, X±5E.M.)

LPLs subpopulations were studied by FACSCAN analysis.Suppressor/cytotoxic T-lymphocytes (CD8+) was significantly (P<0.05) increased in H. pylori positive subjects, (28±5.1 (n=12) vs 20.82±1 (n=12) %. X±5E.M.) and caused a significant difference in the number of helper T-lymphocyte (CD4+) in two groups.

IFN-\gamma production by LPLs was significantly (P<0.05) lower inH. pylori positive patients (31.62±5 (n=10) vs 46.2±4 (n=10) (U/ml, X±5E.M.)) after stimulation with H. pylori. However IFN-\gamma did not differ in LPLs cultured with either PHA, OKT3 or RPMI control.

This may indicate either antigen-specific suppression, in peripheral blood or gastric lamina propria lymphocyte response to H. pylori antigens. IFN-\gamma production decreased in H. pylori positive individuals. IFN-\gamma appears to have an important regulatory role in immune response. Antigen-specific CD8+ suppressor cells within the lamina propria may be responsible for inattenuated responses to H. pylori.

T121


Departments of Medicine and Medical Microbiology, University of Liverpool, and The Trinity College, University of London, UK.

In previous studies we have shown that occasional strains of H. pylori secrete a fucosidase and have speculated that this may have the ability to convert blood group secretors to non-secretors at the mucosal level. Fucosidase and glycosidase production has now been studied in relation to possession by H.P. of the 120 kDa, ulcer-associated antigen.

H.P. were isolated from gastric biopsies, cultured, harvested, washed and suspended in normal saline, the cell walls being disrupted by ultrasonication. Following centrifugation the supernatant was assayed for enzyme activity using methylumbelliferone linked substrates. Nine different strains of H.P. were studied, four being positive for the 120 kDa protein. H.P. did not produce any detectable N-acetyl-b-D-glucosaminidase, b-D-galactosidase, or b-D-glucuronidase. However, one out of the five negative strains and one out of the four positive strains produced an a-L-fucosidase (mean 0.22±S.D. 1.52 U/I/mg protein). A neuraminidase (sialidase) was found in 2/6 (S.D. 1.52±S.D. 1.61 U/I/mg protein) were produced by all nine strains.

The production of sialidase is typical of many other enteropathogens. If data from strains not typed for the 120 kDa antigen are included, significant fucosidase has been demonstrated from 5/21 H.pylori strains. Its production clearly does not correlate with the presence of the 120 kDa protein but further studies are indicated to determine whether it may be an additional marker of pathogenicity.

T122

INTERLEUKIN-6 IS A PROGNOSTIC INDICATOR OF MORTALITY IN SEVERE INTRA-ABDOMINAL SEPSIS. A. Patel, D. Youngs, R.B. Nealeigh. Dept of Surgery, University of Birmingham, UK.

Severe intra-abdominal sepsis is still responsible for a significant mortality and the outcome is not readily predictable. The Acute Physiological and Chronic Health Evaluation Score (APACHE II) of predicting outcome has several drawbacks. IL-6 is known to be elevated in sepsis but little is known of its quantitative role in sepsis.

Our aims were to compare the Apache II scoring system with levels of serum IL-6 (sIL-6) in predicting outcome in severe intra-abdominal sepsis. 29 patients with severe intra-abdominal sepsis were studied. Blood was taken for cytokine levels before, or within one day of antibiotic administration and also measured serially using an Elisa.

There were 8 (28%) deaths. Serum IL-6 levels were detectable in all patients. The sIL-6 levels were >2,000 pg/ml in 7 (88%) of the 8 patients who died (Chi square = 19.85, P<0.001). The death in a patient who had low sIL-6 levels was from a myocardial infarction and not sepsis. The sensitivity of sIL-6 in predicting mortality was 87.5 % and specificity 92.3 % and is thus a better predictor of adverse outcome when compared to the APACHE II score. Elevated serum TNFα and IL-1 beta levels were detected in 4 and 6 patients respectively and did not correlate with mortality.

IL-6 is a pleiotropic cytokine which plays an important role in severe intra-abdominal sepsis as levels are always elevated and serum values >2,000 pg/ml indicate a poor prognosis. Serum IL-6 determination on a routine basis may help in planning future strategies to decrease the mortality associated with sepsis.
Small bowel  T123–T125


Introduction. Studies of the immunogenetics of coeliac disease across ethnic groups suggest that a HLA DQβ1 heterodimer encoded by the alleles DQA1*0501 DQB1*0201 in either a cis- or trans-conformation is closely associated with disease susceptibility. These alleles are however common in the healthy control population, and this hypothesis does not explain the occurrence of DR4-ve coeliac disease. Examination of alleles at the lactase mRNA in HLA haplotypes have not conclusively demonstrated any additional susceptibility influences. The discovery of polymorphic genes located close to the DQ loci, which are involved in processing and HLA loading, may suggest an alternative susceptibility locus.

Methods. In view of the predominance of the B8-DR3 haplotype in Northern Europe and America, the study groups were selected from populations with a high incidence of DR3-ve coeliac disease. 43 Italian coeliac patients (DQA1*0101 DQB1*0201 92%; DR3 51%, DR7 77%, DR5/5 33%) together with 41 ethnically matched controls from Rome, Italy and 34 Ashkenazi Jews with coeliac disease (DQA1*0101 DQB1*0201 78%; DR3 44%, DR7 47%, DR4 26%) together with 35 ethnically matched controls from Rehovot, Israel were studied. Polymorphisms of the TAP 2 alleles were examined using ARMS PCR to detect nucleotide substitutions encoding amino acid residues 665, 656 and 379 respectively.

Results. No significant associations with coeliac disease were found. When analysed with HLA Class II alleles, some skewing of TAP 2 alleles was seen with certain DR types indicating that linkage disequilibrium may exist between these loci, although the association was low between DR-DQ loci.

Conclusion. Coeliac disease is not associated with polymorphisms of the TAP 2 gene. This locus is situated between DQB and DPB loci, with DQB1 localized 150 kb telomeric and TAP 1, the proteasome inhibitor (RING 10 and 12) and DBP1 located centromerically. This study suggests that the susceptibility locus for coeliac disease lies telomeric to TAP 2.

INTESTINAL LACTASE PERSISTENCE

C.B. Harvey*, Y. Wang*, R. Barton#, W. Thurwell*, S. Lanzon-Millar*, R. Loke#, L. Hughes*, D.M. Swallow*, V.R. Sans* & M. Sarner#. MRC Human Biochemical Genetics Unit, UCL* and Departments of Gastroenterology and Histopathology*, Faculty of Clinical Sciences, University College London, Gower Street, London WC1.

Intestinal lactase activity declines after weaning in the majority of people but in some are persistent into adult life. This difference is genetically determined but its precise molecular basis is unknown and there is controversy about the levels of lactase mRNA in persistent and non-persistent individuals. Genetic differences between individuals, polymorphism was found. The lactase protein (apparently M, 150,000) was readily detectable in the samples from the persistent individuals. Samples from the lactase non-persistent individuals showed negligible amounts of this protein although the SI protein was detectable as usual. No evidence was found for an abnormal lactase protein in these individuals.

The level of lactase mRNA was much more variable than the level of SI mRNA both in the persistent and non-persistent individuals, in agreement with the results of Sebastio and colleagues. However, the mean level of lactase mRNA was lower in the non-persistent individuals than the persistent individuals.


Absorption of dietary calcium by the vitamin D-dependent transcellular pathway is greatest in the proximal small intestine. The energy-dependent step in this process is extrusion of calcium at the basolateral membrane by the Ca2+ ATPase and activity of this Ca2+-pump has been shown in the rat to be highest in duodenal villous cells. Four genes (PMCA1–4) coding for plasma membrane Ca2+-pumps have been described and further diversity is produced by alternative splicing of the transcripts, resulting in pump proteins with different regulatory regions. Our previous work showed only PMCA1 and PMCA4 in human intestine and we have now used specific DNA probes to these forms to estimate the distribution of transcripts in different regions of the rat gastrointestinal tract. RNA preparation and Northern blotting followed standard techniques taking care to avoid problems with RNA degradation. Two sizes of transcript for PMCA1 were demonstrated in stomach, small and large intestine. A single, large transcript was detected with the probe with which we have described as the rat form of PMCA4. Separation of small intestine into mucosal and muscle layers showed that PMCA1 was the overwhelmingly predominant form in the mucosa while PMCA4 was the predominant form in the muscle. Division of the small intestinal mucosa into six regions demonstrated that the duodenum had the highest amount of PMCA1 and the jejunum the lowest. This distribution is similar to that found for Ca2+-pump activity, expression of the cytoplasmic Ca2+ transport protein, calcinulin-D96, and for Ca2+ absorption. These results suggest that PMCA1, which has previously been thought to have a ‘housekeeping’ role, is the isoform of the plasma membrane Ca2+-pump which is concerned with calcium absorption.


Nitric oxide (NO) maintains vascular integrity in endothelin-induced acute intestinal damage, but its role in maintaining basal small intestinal physiological function and its relation to blood flow has not been studied in vivo. We have investigated the implications of NO synthase inhibition on physiologic and histologic changes in rat jejunum in vivo. The NO synthase inhibitor nitro L-Arg methyl ester (L-NAME) (100mg/kg) was administered sc to male adult Wistar rats. 20min later a 25cm segment of jejunum was perfused in vivo with iso-osmotic saline containing [14C]-PEG. After 30min of perfusion, 3x10^6 cells of the effluent were obtained to assess water movement. Samples of small intestine were taken at the end of the experiments for histopathologic examination. In a parallel group of animals, L-Arg or D-Arg (500mg/kg) was given sc 15min prior to L-NAME injection. Controls were given either L-Arg, D-Arg or saline without L-NAME. Marked water seepage occurred after L-NAME administration (median -34µl/min/g dry intestinal weight [interquartile range -5 to -18], n=10) as compared with untreated animals (median -6µl/min/g, n=10). This seepage was significantly altered by pretreatment with L-Arg (-17 to -6), n=5; p<0.05 compared to L-NAME alone, but not with D-Arg (-51 to -19), n=5; NS). L-Arg or D-Arg alone had no effect on basal water movement (30 [14 to 38] and 25 [15 to 28] respectively, n=5). Histologic activity was macroscopic and microscopic intestinal ischaemia with vascular congestion and haemorrhage accompanied by early degenerative changes of the surface epithelium. These changes could be prevented with pretreatment with L-Arg but not D-Arg.

Thus, NO appears to play an important role in maintaining small intestinal physiologic function and circulation and its inhibition leads to severe bowel ischaemia and water seepation.

http://gut.bmj.com/content/34/1_suppl/S21
http://doi.org/10.1136/gut.34.1.S21

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IMPAIRED SPLENIC FUNCTION IN PATIENTS WITH INTESTINAL FAILURE ON LONG TERM INTRAVENOUS NUTRITION (IVN). G Zoli, GR Corza, S Wood, MJG Farthing. St Bartholomew’s & St Mark’s Hospitals, London, UK & I Medical Pathology, University of Bologna, Italy.

Impairment of splenic function occurs in medical conditions, including intestinal diseases. This predisposes to infection, including overwhelming septicaemia as in splenectomised patients. Parenteral administration of long chain triglyceride emulsions may have deleterious effects on reticuloendothelial system function which could be relevant to patients on long term IVN. We examined splenic function in 20 patients receiving IVN for at least 6 months (median 56.8, range 6-138), due to short bowel (8 Cronin’s disease, 5 visceromyopathy or neuropathy and 7 miscellaneous conditions), 50 healthy controls and 20 disease controls (unoperated patients, Cronin’s disease who were not receiving IVN) were also studied. Splenic function was evaluated by counting the percentage of pitted red blood cells (PRC) (normal <4%) Nutritional status was assessed as percentage of ideal body weight (IBW%).

Of IVN patients, 17 (85%) were hypocalciemic, of whom 15 had had lipid infusion. Of the 3 with normal PRC count, one had received IVN for only 10 months and two had been continuously treated with vitamin B complex. PRC counts in IVN patients (median 8.0, range 2-16.5%) were greater than in healthy (0.6, 0.3-1.8%; p<0.001) and disease controls (0.9, 0.5-2.0%; p<0.001). No difference was found between healthy and disease controls PRC count increased with duration of IVN (r=0.61; p<0.01). There was no relationship between PRC count and type of disease, IBW%, residual length of small intestine, or administration (quantity and frequency) of lipid emulsion. Eight IVN patients had serious infections (5 septicaemia) within the last 12 months, not related to the central line.

These data suggest that: i) patients with short bowel treated with long term IVN have impaired splenic function with an increased infection risk; ii) this deficit is not obviously related to the primary disease or to the administration of lipid, but to the duration of parenteral nutrition.

COLONIC SECRETORY EFFECT IN RESPONSE TO ENTERAL FEEDING IN MAN. T E Bowリング, A H Raimundo, D B A Silk. Department of Gastroenterology, Central Middlesex Hospital, London, UK.

The pathogenesis of enteral feeding related diarrhoea remains unclear. Our previous studies in normal subjects have shown that it occurs more commonly during intragastric than intraduodenal feeding, and is more likely to result from disturbed colonic rather than small intestinal function. The aim of this study was to investigate the effect of continuous enteral feeding on segmental colonic water absorption.

12 healthy volunteers were intubated with a 9-umen oral tube to the hepatic flexure, 6 were then intubated with a nasogastric feeding tube and 6 with a nasoduodenal tube. The colonic was irrigated with normal saline, and then infusions of H PEG and 14C PEG were started into the terminal ileum and caecum respectively. Steady states of absorption were achieved after 2 hours, after which 3 10 min aspirates were taken proximal to the ileocaecal valve, at the hepatic flexure and from the rectal effluent to establish fasting colonic in-flow volumes and water flows in the ascending and distal colon. A polymeric enteral diet was then infused at 1.39ml/min (1.39kcal/min, 8.75mg/min) for 6 hours, during which aspirates were taken every 20 min from the same 3 ports. Water movement Site of feeding p value

Colonic

Fasting

In-flow:

Fed

0.3(0.1)

1.8(0.2)

<0.001

Ascending colon:Fasting

+0.7(0.1)

+0.9(0.1)

NS

Distal colon:Fasting

+0.6(0.1)

+1.0(0.1)

<0.05

Distal colon: Fed +2.3(0.4)

+1.5(0.1)

<0.05

Mean(SE) + = net absorption - = net secretion

A net secretion of water in the ascending colon has been recognised during intragastric enteral feeding. This response may play an important role in the pathogenesis of enteral feeding related diarrhoea.
A MODEL OF SMALL INTESTINAL NEOUMUCOSAL GENERATION BY THE TRANSPLANTATION OF STEM CELLS. Tait IS, Evans GS*, Flint N*, Campbell FC. University Dept. of Surgery, Ninewells Hospital, Dundee and Dept. of Epithelial Biology, Paterson Institute, Manchester.

Small intestinal epithelium is continuously renewed by multipotent crypt stem cells, which also have potential for extensive mucosal repair following injury. Small Intestinal Stem Cells (SISCs) may therefore have potential for neumucosal formation, provided generative capacity is maintained after stem cell isolation. We describe a novel model of SISC isolation and transplantation, which results in the generation of small intestinal neumucosa.

Method: Cellular aggregates containing SISCs, were isolated from postnatal rat small intestine by Collagenase and Dispace enzymatic digestion, then transplanted subcutaneously into 100 adult inbred rats. All grafts were retrieved after 14 days. Cell proliferation was assessed by autoradiography. Stem cell lineage studies used alkaline phosphatase to identify absorptive enterocytes, Alcian blue for goblet cells, and polygonal antibodies against lysozyme and serotonin to identify Paneth cells and entero-endocrine cells.

Results: 80 successful SISC transplants developed into intestinal structures comprised of a central mucin filled lumen surrounded by neumucosa with well formed crypts and villi. Proliferative cells were limited to basal crypt regions, as occurs in normal small intestine. Lineage studies identified all SISC progeny within the neumucosa i.e. enteroendocrine cells, goblet cells, Paneth cells and endocrine cells.

Conclusion: Postnatal SISCs have the capacity to generate small intestinal neumucosa after isolation and transplantation to apical sites of adult recipients. This neumucosa has typical small intestinal phenotype, and exhibits all stem cell lineages. Neumocosal generation by SISC transplantation is feasible, and may prove a novel method of small bowel mucosal expansion or replacement. This grafting model should also enable further study of environmental factors controlling intestinal stem cell function.

H pylori stomach/duodenum T133-T146


Production of oxygen-derived free radicals(CODR) is increased in inflamed human gastric antral mucosa (out 1991:32:AS64). Levels of vitamin E, a water-soluble antioxidant, are reduced in the gastric juice of subjects with chronic gastritis(Gastroenterology 1986;90:375-6). Alpha-Tocopherol (α-T) is the major active component of vitamin E, and an important lipid-soluble antioxidant. To date there is no information on α-T in human gastric juice. The aim of this study was to measure α-T levels in patients with and without chronic antral inflammation. Mucosal biopsies were obtained from the gastric corpus and antrum of patients undergoing routine endoscopy for dyspepsia. Endoscopic findings and histological criteria(Sydney system) were used to divide the patients into: i)normals (ii)chronic antral- and pre-duodenal gastritis(CAPG). Activity of CODR was determined by neutrophil infiltration(graded on a scale of 0-3). Tissue homogenate and plasma samples were assayed for α-T levels; plasma was also assayed for a marker of CODR activity, thiobarbituric acid reactive substances(TBARS). Dietary vitamin E intake was assayed by means of a food-frequency questionnaire.

<table>
<thead>
<tr>
<th>RNT</th>
<th>NORMALS</th>
<th>CAPG(all)</th>
<th>CAPG(active)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25±5</td>
<td>3±2</td>
<td>9±2</td>
<td>16±0.5</td>
</tr>
</tbody>
</table>

Femtovolts

Determination of plasma TBARS with α-T, was performed after enzymatic digestion for 4h. Plasma TBARS levels were normalized against functional neutrophil counts. The result was: Plasma TBARS levels with neutrophils were 12.0±1.0 fmol/ml. Plasma TBARS levels in CAPG were 17.0±2.0 fmol/ml. In normal stomach plasma TBARS was 5.0±0.5 fmol/ml.

<table>
<thead>
<tr>
<th>RNT</th>
<th>NORMALS</th>
<th>CAPG(all)</th>
<th>CAPG(active)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10±2</td>
<td>7±0</td>
<td>24±2</td>
<td>31±1</td>
</tr>
</tbody>
</table>

Plasma α-T levels

In normal stomach plasma α-T was 5.0±0.5 nmol/ml. In CAPG plasma α-T levels were 9.0±2.0 nmol/ml. In normal stomach plasma α-T was 5.0±0.5 nmol/ml.

<table>
<thead>
<tr>
<th>RNT</th>
<th>NORMALS</th>
<th>CAPG(all)</th>
<th>CAPG(active)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67±1</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Neumucosal generation by SISC transplantation is feasible, and may prove a novel method of small bowel mucosal expansion or replacement. This grafting model should also enable further study of environmental factors controlling intestinal stem cell function.
**T135**

**ANTRAL NODULARITY: A MACROSCOPIC MARKER FOR HELICOBACTER PYLORI GASTRITIS**

**Dr. J. Griller, Dr. P. Tanner, Dr. S. J. Granger**

**DEPT OF MEDICINE, KING GEORGE HOSPITAL, EASTERN AVENUE, ILFORD, ESSEX**

The presence of Helicobacter Pylori (H.Pylori) histologically in chronic gastritis is well recognised, however the relationship between gastric mucosa morphology and H.Pylori colonisation is not established. It has been suggested that this relationship exists it would be useful to the clinician in simplifying the diagnosis of H.Pylori gastritis. We sought to establish a relationship between nodularity of the gastric antrum and the presence of H.Pylori.

**METHODS:** Patients presenting for routine upper gastrointestinal endoscopy were studied. Patients with peptic ulcer disease, duodenitis, neoplasia, or oesophageal pathology were excluded. 53 patients were included in the study over 4 months. The endoscopist noted the presence or absence of antral nodularity which was defined as a regularly undulating mucosa with a cobblestone appearance. Two antral biopsies were taken one for a CLO-test and one for histological examination. Colonization of mucosa by H.Pylori was defined as either CLO-test positive and/or histological presence of H.Pylori.

**RESULTS:** Relationship between Histology & CLO-test

<table>
<thead>
<tr>
<th>CLO +ve</th>
<th>CLO -ve</th>
<th>Total</th>
<th>Sensitivity of CLO-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>3</td>
<td>19</td>
<td>84.2%</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>34</td>
<td>23.5%</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>29</td>
<td>53%</td>
</tr>
</tbody>
</table>

Relationship between Antral Nodularity & Mucosal Colonization by H.Pylori

<table>
<thead>
<tr>
<th>Colonization</th>
<th>Nodular Smooth</th>
<th>Total</th>
<th>Sensitivity of H.Pylori</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>20</td>
<td>7</td>
<td>77%</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>26</td>
<td>26%</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>33</td>
<td>53%</td>
</tr>
</tbody>
</table>

**CONCLUSIONS:** Nodularity of the gastric antrum is a specific marker of mucosal colonization by H.Pylori. We would suggest that in the presence of antral nodularity H.Pylori colonization may be assumed, thus avoiding the need for additional biopsies.

**T136**

**ERADICATION OF HELICOBACTER PYLORI INFECTION LOWERS GASTRIN-MEDIATED ACID SECRETION BY 50% IN HEALTHY VOLUNTEERS**

**E. E. El-Omar, L. Penman, J. E. S. Ardill, B. W. McEl, McColl. University Department of Medicine & Therapeutics, Western Infirmary, Glasgow and Queen’s University, Belfast.**

We have previously demonstrated that gastrin-mediated acid secretion induced by the IV administration of gastrin releasing peptide (GRP) was increased 6-fold in DU patients with H. pylori infection and 3-fold in healthy volunteers with H. pylori infection, compared to healthy volunteers without H. pylori infection. Eradication of H. pylori lowered acid secretion by 66% in DU patients. The present study was undertaken to assess the effect of eradication of H. pylori on gastrin-mediated acid secretion in the healthy volunteers.

**METHODS:** 11 healthy volunteers with H. pylori infection (7 males) were studied. Following a basal period of 45 minutes, GRP was infused at 40μmol/kg/h. Blood samples for gastrin determination and gastric juice for acid output were collected every 15 minutes throughout the study period. The same test was repeated one month following completion of a three week course of anti-H. pylori triple therapy.

**RESULTS:** The median gastrin concentration during GRP infusion pre-treatment was 238ng/l (range: 50-420) and fell to 45ng/l (range: 25-295) (p<0.008) following eradication of H. pylori. The median acid output during GRP infusion pre-treatment was 15.2mmol/l (range: 10.3-38.3) and fell to 8.8mmol/l (0.8-21.0) (p<0.005) following eradication, representing a median fall of 50% (95% confidence interval: 30% to 70%). The median acid output following eradication was similar to that obtained in healthy volunteers who never had H. pylori infection (median = 6.9, range: 1.0-9.0) (p=0.3).

**CONCLUSIONS:** In healthy volunteers, eradication of H. pylori lowers gastrin-mediated acid secretion by 50%. Permanently reducing acid secretion by eradicating the infection may be of value in the wide range of upper GI disorders currently managed with acid lowering drugs.

**T137**

**DUODENAL HISTOLOGY, ULCERATION, AND HELICOBACTER PYLORI IN THE PRESENCE OR ABSENCE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID)**

**A. S. Tari, K. NAEHABERsi, R. E. STURMOTT, R. I. ROSELL**

**DEPARTMENT OF GASTROENTEROLOGY AND RHEUMATOLOGY, ROYAL INFIRMARY, GLASGOW, UK.**

Gastric histological studies in chronic NSAID users have identified a characteristic picture known as chemical gastritis (Tari et al., 1992) which correlates strongly with gastritis ulceration. Little is known about the duodenal microstructure in such patients.

We aimed at identifying the duodenal histological abnormalities in the presence or absence of NSAID, duodenal ulcers, and H. pylori.

**METHODS:** Endoscopic biopsies were taken from healthy looking mucosa in the duodenal bulb and gastric antrum of 172 patients (74 took NSAID and 98 did not). Duodenitis was graded according to the degree of neutrophilic and plasma cell infiltration, villus height, Brunner’s gland prolapse, and gastric metaplasia. The activity of duodenitis was dependent on the neutrophilic infiltration. H. pylori was assessed in both the stomach and duodenum by culture and histology. All specimens carried code numbers.

**RESULTS:** Duodenitis with varying degrees of neutrophilic infiltration and gastric metaplasia was found in 20 patients (27%) taking NSAID, compared with 56 (57%) not on NSAID (χ²=41.26, p<0.001). Duodenitis was also found in 20 out of a total of 25 patients (80%) with duodenal ulcers, regardless of NSAID intake (χ²=15.38, p<0.001). Duodenal H. pylori was only seen in patients with gastric metaplasia (10/20, 50%) on NSAID and 34/38, 8% not on NSAID). H. pylori, positive gastritis, and both active duodenitis and gastric metaplasia were independent predictors of duodenal ulcers.

**Conclusion:** Active duodenitis is less common in NSAID patients, but is strongly associated with gastric metaplasia, H. pylori, and duodenal ulcers. This however, does not explain all cases of NSAID-related duodenal ulcers, and other mechanisms of damage, such as proton pump inhibition, need to be considered.

**T138**

**GASTRIC MUCOSAL CD3/CD4 LYMPHOCYTES AND ANTIGEN PRESENTING CELLS BEFORE AND AFTER TRIPLE THERAPY FOR HELICOBACTER PYLORI INFECTION**

**J.W. Wyeth, K. E. Eng, A. Fraser, E. Sankey, A. Dhillon, RE. Founder, Dept of Medicine, Royal Free Hospital School of Medicine, London NW3, UK.**

It is hypothesised that persistence of H. pylori in the gastric antrum relies on modulation of the cellular immune system. To determine if eradication of the organism or triple therapy effects gastric intramucosal indices of cellular immunity, 20 male subjects with H. pylori infection (positive CLO-test, positive H. pylori culture test and positive histology) were gastroscoped and antral biopsies taken before and six weeks after triple therapy (De-Nol tabs qid for 14 days, and tetracycline 500 mg qid, metronidazole 400 mg tid for 7 days). Biopsies were formalin fixed, H&E stained for assessment by a single observer for number of Helicobacter-like organisms, activity and inflammation according to the Sydney Classification. Immunostaining of CD3 and CD4 positive cells, antigen presenting cells (APC) and all inflammatory cells were performed on serial sections from the same tissue block. Count of positive cells was by both computer image analysis and by an observer in a blind study design. Results: H. pylori was eradicated in 8/20 (40%) subjects at 6 weeks. Numbers of organisms, activity and inflammation were reduced irrespective of eradication of H. pylori. Median cell counts:

<table>
<thead>
<tr>
<th>CD3</th>
<th>CD4</th>
<th>APC</th>
<th>ALL CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>N</td>
<td>E</td>
<td>N</td>
</tr>
<tr>
<td>Pre</td>
<td>20</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Post</td>
<td>30</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>p-value &lt;0.05</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

**Conclusion:** Triple therapy was associated with an increase in APC numbers irrespective of successful eradication suggesting a drug effect. A significant increase in CD8 cell numbers was detected, implying an increase in the CD8 subset of T-cells. H. pylori infection may suppress CD8 T-cell expression.
HELICOBACTER PYLORI INFECTION INCREASES IN AN ALKALINE ENVIRONMENT AFTER CHOLECYSTECTOMY.

MTP Caldwell, M McDermott, S Jazrawi, PJ Byrne, TN Walsh.
Dept Hepatogastroenterology, T D Hennighan.
University Dept of Pathology and Surgery, St. James’s Hospital, Dublin 8, Ireland.

Antral gastritis is a common finding in patients who remain symptomatic following cholecystectomy and it is felt that this is related to reflux of the alkaline duodenal contents into the stomach. Most authors suggest that Helicobacter pylori(H.pylori) cannot survive in an alkaline environment.

22 patients with documented cholecystitis underwent upper gastrointestinal endoscopy and biopsy and 24 hour dual channel pH monitoring prior to cholecystectomy and again three months postoperatively. The gastric biopsies were histologically assessed for H.pylori and gastritis and awarded an alkaline reflux score.

**Results**

- **Gastric pH > 4**
  - **Pre-op**
    - Median: 9.6 (2.2) % time: 22.2 (4.8)
  - **Post-op**
    - Median: 8 % time: 7
  - *p* value: <0.01

- **Reflux score**
  - Median: 3
  - **(no. patients)**
    - 6: 14
    - 7: 15
- **H.pylori**
  - Median: 3
  - **(no. patients)**
    - 6: 14
    - 7: 15
  - *p* value: <0.005

Postoperatively there was no significant difference in the % time gastric pH>4 between those who were H.pylori positive(6.1±2.7) and those who were negative(1.2±2.9). Postoperatively, however, this was significantly raised in those who were H.pylori(26.7±5.6) when compared to those without(8.3±2.5).

Seven patients remained asymptomatic all of whom were H.pylori positive and had gastritis.

These data contradict the theory that H.pylori cannot survive in an alkaline environment and suggest that it may be a contributory factor in the post-cholecystectomy syndrome.

2. Statistics: Chi squared and Wilcoxon signed and rank sum tests where appropriate.

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**EVALUATION OF A SALIVARY IgG ASSAY TO DETECT H. PYLORI INFECTION**

P Patel, M A Mensell, S Khulasi, N Molineux, T C Northfield.
Dept. of Medicine, St. George’s Hospital Medical School, London.

**BACKGROUND**

Measurement of serum IgG to H. pylori proteins by ELISA is a well established method of assessing H. pylori status. The use of saliva for measurement of IgG to H. pylori has not been fully explored. Salivary IgG is derived from serum and is present at concentrations of about 1/800 to that of serum. We have evaluated the use of salivary IgG in the diagnosis of H. pylori infection.

**SUBJECT & METHODS**

Saliva from 39 dyspeptic patients (20 male and 19 female) was collected prior to endoscopy. H. pylori status was assessed by histology and rapid urease test. The saliva samples were centrifuged at 2000g for 10 minutes to remove debris. The undiluted supernatant was tested, in duplicate, on an Eisa system using an acid glycine extract as the antigen (Helico-Go). Peroxidase conjugated goat IgG, at a dilution of 1/1000, to human Fc IgG was used as labelling antibody. This is normally used at a dilution of 1/3600 when testing serum. The elisa was read at 450 nm.

**RESULTS**

The mean optical density (OD) for positives was 1.263, SD 0.57, and for negatives 0.488, SD 0.18. A cut-off point of 0.750 OD gave a sensitivity of 20/22 (91%) and a specificity of 16/17 (94%).

**CONCLUSION**

Assessment of H. pylori status from saliva is possible and valid. It could be useful for clinical or epidemiological purposes, especially in children.

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**POLYMERASE CHAIN REACTION ASSAY DETECTS THE SITES AT WHICH HELICOBACTER PYLORI EVADES TREATMENT WITH AMOXYCILLIN AND CIMETIDINE.**

JC Allerton, A Cockayne, M Baltitis, CJ Hawkey, RC Spiller, Depts Therapeutics, Microbiology, Pathology, University Hospital, Nottingham NG7 2UH.

Amoxicillin appears to clear H.pylori from the stomach but recurrence is virtually invariable. This implies residual infection at an unidentified site. As H.pylori is usually undetectable by standard tests during amoxicillin treatment we used a polymerase chain reaction assay (PCR) to locate this site.

Methods. 22 patients with duodenal ulcer disease, 18 male, median age 42, range 22-68, had endoscopies before and after 1 week of treatment with amoxicillin capsules 500mg tds (before food) and cimetidine 800mg nocte. One month after finishing amoxicillin patients underwent a "C-urea breath test (UBT). At both endoscopies biopsies were taken from antrum, body (greater curve) and fundus using fresh forceps for each area. Two biopsies from each area were sent for histology (modified Giemsa stain of 3 serial sections), 1 for culture (incubated on chocolate blood agar at 37°C in 6%CO2, for 72hrs) and 1 for biopsy urease (CLO) test and later PCR. PCR used primers for part of the 16S rRNA gene and was specific for H.pylori.

Results. At the end of antibiotic treatment H.pylori was detected by PCR in 16/22 patients and was found in fundus (12) or body (10) more frequently than antrum (3) p<0.05. In all 3 patients in whom H.pylori was detected in antrum it was also found elsewhere (body in 1, body and fundus in 2). In the other 13 patients with positive biopsies H.pylori was found in body alone in 3 patients, fundus in 6 and both in 4. Although H.pylori was not detected in 6 patients final UBT was positive in all. After amoxicillin therapy histology and CLO failed to detect H.pylori but 4 patients were culture positive (all also PCR positive). Before treatment H.pylori was detected in all areas of all stomachs (except fundus in 1 patient) by PCR and at least 1 other test.

Conclusion. H.pylori is usually cleared from the gastric antrum by this amoxicillin/cimetidine combination but frequently evades treatment in the body and fundus.

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**ANTRAL AND FUNDIC SURFACE MUCOSAL pH IN CHILDREN WITH AND WITHOUT HELICOBACTER PYLORI (HP) GASTRITIS**

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Gastric pH can be measured by titration of the aspirated gastric juice or by inserting an electrode into the stomach for 24 hours. However, both methods measure the same net result of secretion and back diffusion of H+.

Using a miniature electrode passed through the biopsy channel of the gastroscope the mucosal surface pH measurement can be directly obtained.

AIM: To study whether alteration of mucosal pH can be found in patients with HP gastritis we measured mucosal surface pH from the fundus and antrum in children, and related them to fasting serum gastrin.

PATIENTS AND METHODS: We studied 79 children (median age 10 yrs, range 2-14) 43 had a normal antral mucosa (controls) 22 had HP gastritis (HP+) and 14 have been studied once after HP was eradicated with amoxicillin and tindazole.

During endoscopy a miniature electrode connected to a portable pH-meter (Digitrapper, Synectics) was positioned against the mucosa until a stable pH reading was obtained at the fundus (for 1 min.) and then at the antrum. Fasting serum gastrin was measured by RIA.

RESULTS: Mean (±SD) fundic mucosa HP was 6.2±1 in controls, 6.5±1 in HP+ children and 6.1±0.9 after HP eradication (differences not significant). Antral pH was 5.7±1 in controls and 6.2±1 after HP eradication, but was significantly increased in HP+ children (6.7±2 p<0.01).

Mean (±SD) serum gastrin was 33.26±24 µm/L in controls and 33.93±18 after HP eradication, but was not significantly related in HP+ children (45±2, p=0.01).

In HP+ children antral pH was significantly related to serum gastrin (r=0.556, p<0.03).

CONCLUSION: In H pylori infected children antral mucosal surface pH and serum gastrin are increased, and significantly related. This is possibly due to ammonia produced by HP urease and might cause the increased gastrin cell number found in these children.
EFFECTS OF ETHNICITY ON H. PYLORI ANTIBIOTIC SENSITIVITY AND DISEASE ASSOCIATIONS

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GI Science Unit, London Hospital Medical College, London E1 2AI.

One third of patients referred for routine upper GI endoscopy in our unit were born in Bangladesh. We compared the prevalence of H. pylori antral infection, the disease-associations of H. pylori-infected cases, and metronidazole resistance patterns between Bangladeshi-born and indigenous Caucasian populations.

Methods: Unselected outpatients (n=229) referred for gastrointestinal were studied for H. pylori prevalence using a commercially available urease test and standard culture technique. Gastric and duodenal damage was graded macroscopically (modified Lanza scale) and microscopically (H and E). A separate group (n=49) was assessed for metronidazole resistance. None had recently received bismuth, omeprazole, metronidazole, or any other antibiotics. Metronidazole-resistant isolates were defined as those having MICs of $\geq$ 8μg/ml, corresponding to a zone $\leq$ 10mm in diffusion tests using 5μg metronidazole discs.

Results: 34% (79/229) patients were born in Bangladesh (Bgs) (mean age: range) 43yrs (16-69); of these 68% were H. pylori (Hp) positive, compared with 46% (p=0.003, chi-squared test) in Caucasians (Ci) (54yrs (15-85)). The prevalence of Hp was higher in Bangladeshi patients in each age cohort: 0-30 yrs, Bg 88%, Ci 23%: 31-50yrs Bg 69%, Ci 40%; 51-70yrs, Bg 69%, Ci 50%: each (p<0.05). Within each cohort, however, the prevalence of DU disease in Hp positive cases was no different: 0-30 yrs, Bg 27%, Ci 33%; 31-50yrs Bg 31%, Ci 36%; 51-70yrs, Bg 26%, Ci 17%; (each p<0.5). Similarly there were no significant differences in the Lanza macroscopic scores or the microscopic gradings between HP positive Bangladeshi and Caucasian patients. Metronidazole-resistant organisms were present in 95% (91/222) Bangladeshis compared with 40% (11/27) Caucasians (p=0.01, Fisher's exact test).

Conclusions: In our catchment area, the prevalence of Hp infection and metronidazole resistance is higher in the Bangladeshi ethnic minority than in referrals from indigenous, UK-born, Caucasian population. The spectrum of disease associated with Hp infecion, however, does not differ between ethnic groups. Knowledge of antibiotic-resistant groups should be used to develop treatment strategies appropriate to the local community.

COMPARISON OF 3, 5, AND 7 DAY TRIPLE THERAPY FOR H. PYLORI ERADICATION.

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The optimum duration of triple therapy for H. pylori (Hp) eradication is unclear. Short courses have the advantages of better patient compliance, lower cost and adverse effect incidence. Study Aim: Comparison of 3 short courses of triple therapy with metronidazole (MZ), Amoxycillin (T), and colloidal bismuth subcitrate (CBS) in Hp eradication and duodenal ulcer healing.

Methods: Three groups of Hp positive patients with endoscopically proven, previously untreated duodenal ulceration were allocated to treatment with MZ 400 mg tds, T 500 mg tds and CBS 120mg qds for either 3, 5 or 7 days followed by CBS alone at the same dose for a total of 28 days. Ulcer healing and Hp eradication were assessed 4 weeks after cessation of therapy. Eradication was confirmed by negative rapid urease test, histology and culture. Results: The groups consisted of 9, 10 and 10 patients in the 3, 5 and 7 day courses respectively. Groups were comparable for age and sex. Ulcer healing rates after 4 weeks were 66%, 60%, and 100% respectively of Hp eradication 5d 7d and 3d <0.05; 5d 7d p<0.05; Hp eradication rates were 33%, 50% and 90% (3d v 5d NS; 3d v 7d p<0.05; 5d v 7d p=0.05). No adverse side effects of therapy were reported.

Conclusion: Seven day triple therapy was associated with significantly higher healing rates for duodenal ulcer and higher eradication rates of Hp than 3 and 5 day treatment courses when combined with extended CBS therapy.

HELCOBACTER PYLORI PYLORI : A COMBINATION OF OMEPRAZOLE, AMOXYCILLIN AND METRONIDAZOLE COMPARED WITH STANDARD TRIPLE THERAPY.

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We have treated 110 H. pylori infected patients with a two week course of Omeprazole (50 mg TDS), Amoxycillin (500 mg TDS) and Metronidazole (400 mg TDS). The results of treatment with OAM are compared with updated figures from our previously published experience with two weeks of standard triple therapy (STT) of bismuth subcitrate, tetracycline and metronidazole. (Aliment. Pharmacol. Ther. 1992,6:327-333).

OAM was better tolerated than STT with 107/110 able to complete the 14 day course compared with only 35/43 treated with STT (p < 0.01). With OAM the H. pylori eradication rate was 94.7% in those with a metronidazole sensitive pre-treatment isolate compared with 70% in the patients whose isolate was resistant to metronidazole. The corresponding eradication rates for STT were 90.9% for metronidazole sensitive infections and 33.3% for resistant organisms.

We conclude that OAM is better tolerated than STT and with metronidazole sensitive organisms both regimens achieve > 80% eradication rates while with metronidazole-resistant infections OAM is significantly (p < 0.05) more effective.
PLATELET DERIVED GROWTH FACTOR STIMULATES ANION SECRETION IN MAMMALIAN COLON. Wardle T.D., Turnbull L.A. Epithelial Membrane Research Centre and Department of Medicine, Hope Hospital, Salford, Manchester, M6 8HD, U.K.

Platelet derived growth factor is released during the inflammatory response and may have an important role in the pathophysiology of diarrhoeal diseases. Its precise mechanism of action however remains in doubt. We therefore investigated the secretary effect and mechanism of action of platelet derived growth factor in mammalian colon.

Rat distal colonic mucosa was mounted as sheets in modified flux chambers and both surfaces were bathed in Ringer's buffer. Changes in transmucosal short circuit current (Isc), potential difference (pd) and conductance were measured following the basaloidal addition of platelet derived growth factor (10^{-16} - 10^{-4}M) in chloride containing or chloride free buffer, in the presence of one of the following (a) indomethacin 10^{-7}M (cyclooxygenase inhibitor), (b) ICI 207968 10^{-7}M (a lipoxigenase inhibitor), (c) combined (a) and (b), and (d) mepacrine 10^{-6}M (a phospholipase A2 inhibitor).

Platelet derived growth factor stimulated an increase in Isc (EC50 = 7 x 10^{-10}M; peak = 41 ± 4.4 μA·cm⁻²) and a modest rise in pd and conductance when added to the basolateral, but not the apical half chamber. This change in Isc was reduced by the omission of chloride (41 ± 4.4 v 14.9 ± 1.9 μA·cm⁻² p<0.005). Pretreatment with either indomethacin (cyclooxygenase inhibition) or ICI 207968 (lipoxigenase inhibition) reduced the Isc (41 ± 4.4 v 28.7 ± 2.9 ; 31.1 ± 3.6 μA·cm⁻² respectively, p<0.01). Moreover, combined pre-treatment produced a greater fall in Isc (41 ± 4.4 v 19.6 ± 1.9 μA·cm⁻², p<0.001), but this was further reduced by mepacrine inhibition of phospholipase A2 (41 ± 4.4 v 12.3 ± 1.4 μA·cm⁻², p<0.005).

In conclusion, platelet derived growth factor stimulates anion secretion in mammalian colon. This action is mediated predominantly by arachidonic acid metabolites, however other phospholipase A2 derivatives, for example platelet activating factor, may also be implicated.

A PROSPECTIVE CLINICAL TRIAL TO DETERMINE THE INFLUENCE OF SULINDAC ON THE FORMATION OF RECURRENT COLONIC ADENOMATOUS POLYPS. AC. D. Fuller, JT Allardice, WM Woods, SP Purslane, A M Ablard, B K Taylor and HS Williams. The Surgical Unit, The Royal London Hospital, LONDON E2.

Patients who develop adenomatous polyps or cancer of the colon and rectum have an increased risk of developing further tumours in subsequent years; such patients are advised to undergo regular colonoscopy. This imposes strains on endoscopic resources and on the patients themselves.

Previous reports have suggested that sulindac, a non-steroidal anti-inflammatory, is associated with suppression of polyp in familial adenomatous polyposis (FAP).

A double blind randomised prospective controlled clinical trial was therefore carried out to determine whether sulindac had any influence on the rate of recurrence of polyps in non-FAP patients. 100 patients who had either undergone surgery for colorectal carcinoma or resection of colonic polyps were randomised to receive either sulindac 200mg bd or placebo. Following pre-entry colonoscopy to exclude the presence of cancer or polyps, colonoscopy was performed at 6 monthly intervals. Metachronous development of a carcinoma or colonic polyp was taken as a positive and point.

49 patients were randomised to placebo and 51 to sulindac. 12 patients withdrew from the placebo arm and 14 from the sulindac arm of the trial. 7 patients taking placebo developed polyps and 6 patients taking sulindac developed polyps. Mean length of follow up was 12.8 months.

No significant difference in the number of patients developing a metachronous polyp or carcinoma was detected between those receiving sulindac and those receiving placebo (Chi squared test). These data suggest that sulindac does not influence the rate of recurrence of adenomatous polyp.

The study was approved by the Towns Heath Authority ethical committee.

COMPARISON OF COLORECTAL CANCER RISK IN CROHN'S DISEASE AND ULCERATIVE COLITIS. C D. Gillen, P Prior, H A. Andrews, R N. Allan, Gastroenterology Unit, General Hospital, Steelhouse Lane, Birmingham, B4 6NH.

The colorectal cancer risk was compared in two identically selected cohorts of patients with Crohn's disease (N=281) and ulcerative colitis (N=823). All known features which might bias the estimate were eliminated.

For each series as a whole, there was a three-fold excess risk of colorectal cancer in Crohn's disease and an eight-fold risk in ulcerative colitis. The difference is probably explained by a significantly increased risk of rectal carcinoma in the ulcerative colitis group. Dividing each series by extent of colitis, patients with extensive colitis showed an eighteen-fold increase in risk in Crohn's disease and a nineteen-fold increase in risk in ulcerative colitis. The risk decreases with increasing age at onset in both groups. The absolute cumulative frequency of colorectal cancer in extensive colitis was 8% at 22 years from onset in the Crohn's disease group and 7% at 28 years from onset in the ulcerative colitis group.

These results demonstrate for the first time that the risk of colorectal cancer in extensive colitis is similar for Crohn's disease and ulcerative colitis. Young age at onset is an important risk factor in both groups. The absolute number of patients with Crohn's disease developing colorectal cancer is small because most patients with extensive Crohn's colitis undergo surgical excision relatively early for symptomatic disease.
**T151**

**INCREASED SECONDARY DUODENAL BILE ACIDS IN PATIENTS WITH COLONIC CANCER.**


University Department of Surgery, Dudley Road Hospital, Birmingham B18 7QH and *Clinical Mass Spectrometry Unit, Northwick Park Hospital, Middlesex HA1 3UJ*

It has been proposed that alterations/differences in bile acid metabolism are important in colorectal carcinogenesis. We studied the duodenal bile of 41 patients with colorectal cancer (CRC) (20M, 21F), 15 with adenomatous polyps (10M, 5F) and 39 controls (18M, 21F) (p=0.001). Bile was collected at upper GI endoscopy and before any surgery. Glycine and taurine conjugated bile acids were analysed by gas liquid chromatography. Patients with CRC were found to have increased proportions (t test) of biliary lathocholic (0.99, 0.6-0.98) (median, range) and 3α-hydroxy, 12-keto-5α cholic acids (1.99, 0.14-1.85) when compared with both control (0.5, 0.4-0.85, P=0.039) and 0.94, 0.6-4, P=0.03 respectively) and polyp patients (0.53, 0-2.86, P=0.049 and 0, 0-3.28, P=0.009 respectively).

Following exclusion of patients with gallstones, cholecystectomy or hepatic metastases, 28 patients with CRC were found to have increased proportions of total secondary bile acids (35, 20.7-43.8) when compared with 32 control subjects (30.3, 9.5-53.2, P=0.007) and 14 patients with polyps (26.76, 9.34-41.7, P=0.013). In particular the proportions of deoxycholic acid and its metabolite 3α-hydroxy, 12-keto-5α cholic acid were increased when compared with both controls (19.02, 0-32.35, P=0.009 and 0.75, 0-6.52, P=0.032 respectively) and polyp patients (18.52, 7.66-37.99, P=0.036 and 0, 0-3.23, P=0.009 respectively).

This controlled study demonstrates that patients with established colorectal cancer exhibit an altered bile acid metabolism/absorption when compared with both control and polyp patients.

[Statistics: Kruskall-Wallis and Mann Whitney U Tests]

**T152**

**LOW DOSE o-3 FATTY ACID SUPPLEMENTATION REDUCES RECTAL EPITHELIAL CELL PROLIFERATION IN PATIENTS AT RISK FOR COLON CANCER.**


Istituto di Clinica Medica, Univ. Catolica, Lago F. Vito I, Rom, *Biologia, Univ. Tor Vergata di Roma, **Patologia Medica, Univ. di Modena, Italy.*

We have shown (Gastroenterology 1992;103:883-91) that high-dose o-3 fatty acids supplementation (fish oil) reduces cytokinin anisotropies in the flat rectal mucosa of sporadic colorectal adenoma patients. To evaluate the dose/effectiveness relationship of this potential chemopreventive agent, a randomized, double-blind, placebo-controlled study was conducted on 60 patients with sporadic colorectal adenomas. Patients were randomly assigned to Group A (which received 2.5 g fish oil/day; eicosapentaenoic acid (EPA) 1.4 g/day + docosahexaenoic acid (DHA) 1.1 g/day), Group B (5.1 g fish oil/day: EPA 2.7 g + DHA 2.4 g), Group C (7.7 g fish oil/day: EPA 4.1 g + DHA 3.6 g) or Group D (placebo); the patients followed standard Mediterranean diets during the trial. Before and after 1 month of supplementation, flat rectal mucosa was endoscopically biopsied to assess proliferative activity (3H-Thymidine autoradiography) and fatty acid content (gas liquid chromatography). In proliferation studies, a total labeling index (TLI), i.e. ratio of labeled (5-phase) to total cells, was calculated for each well-oriented hemi-mucosa. The hemi-mucosa was also divided into five equal cell compartments from base (compartment 1) to mouth (compartment 5) to evaluate longitudinal distribution of labeled cells. ANOVA was used for statistical analysis. Plasma fatty acid data indicated good overall compliance with advice. After 1 month, significant (F=26.25 P<0.01) almost identical TLI reductions were found in the 3 fish oil groups (Group A: 10.4±1.35 7.6±0.4; Group B: 10.3±0.7 6.4±0.5; Group C: 10.7±0.17 7.7±0.2). Reduced labeling index were for all compartments, was more marked in the upper crypt compartments 4-5, as shown by analysis of changes (D) (F=2.9; P=0.04). No proliferative changes were noted in the placebo group. Dose-dependent increases in rectal mucosal EPA and DHA levels were noted in fish oil groups. Low dose supplementation seems to be as effective as high dose supplementation in normalizing rectal mucosal proliferation in patients at risk for colon cancer. Use of lower doses should reduce the risk of adverse effects in long-term chemopreventive trials conducted in large numbers of patients.

*Supported by grant CNR PFO ACRO n° 92.02132. FF39.*

**T153**

**PHOTODYNAMIC THERAPY FOR VILLOUS ADENOMAS OF THE RECTUM AND COLON.**

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Colorectal villous adenomas should be surgically excised in view of their premalignant potential. When surgery is not possible, endoscopic thermal laser therapy has been used with some success although reported series indicated quite a high recurrence rate which is most likely due to incomplete tumour ablation because of risk of perforation Photodynamic therapy (PDT) involves the low power light activation of a light sensitive but otherwise non-toxic drug (photosensitiser) which accumulates in tumour tissue following administration. This light-drug interaction produces cytotoxic chemical species resulting in tissue necrosis. As only low power light is used, no thermal effect is produced. PDT has been shown not to compromise colonic bursting strength even after full thickness injury and tumours can be treated deep without fear of bowel perforation. Eight patients with 9 villous adenomas (recorded disease duration 2-30 months; mean=12.8) were treated with PDT using either haematoxyphilin derivative (2.5 mg/kg) or Photofrin (2 mg/kg) as photosensitiser and multiple applications (4-16; mean=9) of interstitial photoradiation with red light (630 nm, 100 mW x 500 sec) at approximately 1 cm apart. All but one adenomas were in the study were recurrent lesions following Nd-YAG laser therapy (total of 66 treatment sessions). Adenomas size ranged from approximately 2 x 2 cm to 5 cm long extending % of the circumference. Cutaenous sensitivity to sunlight was seen in one patient. PDT resulted in eradication of seven adenomas (follow up 3-50 months; mean=17.1). No local complication was seen. Two bulky adenomas were not eradicated although substantial necrosis was produced. This pilot study indicates that PDT following prior debulking using Nd-YAG laser may be highly effective in eradicating sessile villous adenomas.

**T154**

**CARCINOMA OF THE LOWER GASTROINTESTINAL TRACT IN CROHN’S DISEASE.**

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Introduction: An increased incidence of carcinoma affecting the small and large intestine has been described in patients with Crohn’s disease, though its extent remains disputed. Carcinoma developing in long standing anorectal disease is uncommonly reported. The 53 experience of lower gastrointestinal malignancy in patients with Crohn’s disease was established by clinical, radiological, endoscopic or pathological features. The details of patients who no longer attended the hospital were not available.

Results: 2 patients developed carcinoma of the colon; their history of Crohn’s disease was 2-72 months. One had a rectal adenoma; neither had dysplasia. 13 patients developed 15 carcinoma of the rectum or anus (10 adenocarcinomas, 5 squamous cell). All of these patients had long standing anorectal disease (proctitis 2, stricture 4, abscesses 2, fistula 4, tags 1). 10 carcinomas were in the rectum; 1 in the upper third, 2 in the middle third and 7 in the lower third. Dukes staging for these rectal carcinomas included A2, B7, C1; concomitant dysplasia was present in four. There were 4 anal tumours and one in an anus. Carcinomas were treated by local excision or biological therapy. In 4 cases.

Conclusion: The incidence of carcinoma in Crohn’s disease was less than might be expected in the general population, despite our practice of routine debulking of disease and low surgical rate. Our results suggest that routine surveillance of patients with colonic Crohn’s disease is not justified. In contrast, patients with long standing anorectal Crohn’s disease, especially if complicated, appear to be at increased risk for anorectal cancer, and monitoring with endoscopy and biopsy of this region would seem appropriate.
A RANDOMISED TRIAL OF FLEXIBLE SIGMOIDOSCOPY AND HAEMOCCULT VS HAEMOCCULT ALONE IN COLORECTAL CANCER POPULATION SCREENING

MHE ROBINSON, DP BERRY*, KD VELLACOTT**, V MOSHIKIS***, JD HARDCASTLE

Departments of Surgery, University Hospital, Nottingham; * University Hospital of Wales, Cardiff; ** Royal Gwent Hospital, Newport; *** George Eliot Hospital, Nuneaton.

50% of colorectal cancers detected by Haemoccult (H/O) screening are at Stage A. However, of subjects completing the tests and found to have cancer, 30-50% have presented symptomatically following a negative result. 63% of these were located distal to the splenic flexure and could have been detected earlier by flexible sigmoidoscopy.

The aim of this study was to compare the compliance, positive rate and yields of flexible sigmoidoscopy (F/S) and H/O screening versus H/O alone. 1991 subjects aged 50 to 74 were randomly allocated to F/S and H/O (Group I, n=958) or H/O alone (Group II, n=1033). No dietary restrictions were imposed. Any subject with a positive H/O test or a neoplasm found at F/S was referred for colonoscopy. In Group I, a total of 457 (47.7%) completed H/O tests and 11 (2.4%) were positive (2 cancers, 9 adenomas detected). 270 (28.2%) accepted F/S, of whom 14 patients (5.2%) had 22 adenomas (11 ≥ 1 cm) and one cancer. In Group II, 14 (2.4%) of the 573 (55.4%) completing tests had a positive reaction (1 cancer, 3 adenomas detected). Subjects in Group I (59.4 per 1000 screened) had significantly more neoplasms detected than those in Group II (7.0 per 1000 screened)(p<0.001).

The additional yield of flexible sigmoidoscopy over Haemoccult is encouraging, but methods of invitation to improve compliance to flexible sigmoidoscopy are needed.

SEGMENTAL TRANSIT STUDIES DEFINE A REGIONAL DELAY IN PATIENTS WITH POSTCHILDHOOD/HYSTERECTOMY CONSTIPATION & Macdonald, F Poorm, JN Barker, IS Finlay

University Department of Surgery & Department of Radiology, Royal Infirmary, Glasgow

Patients who attribute their constipation to childbirth or hysterectomy may have a hindgut neuropathy alone with delay confined to the left colon. Demonstration of a regional dysmotility would select patients suitable for segmental as opposed to total colonic resection. Accordingly segmental colonic transit was measured in patients who developed their symptoms after childbirth or hysterectomy and compared with age-matched controls.

Patients (n=12) and controls (n=16) swallowed 20 radio-opaque markers on 3 consecutive days. A plain abdominal film was taken on day 4 and using a standard formula, transit through the right, left and rectosigmoid colon was measured. Results were analysed using Mann-Whitney-U test. Approval for the study was granted by the Hospital Ethical Committee.

Results

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<th>Transit (hours)</th>
<th>Mean (±st dev)</th>
<th>Controls</th>
<th>P</th>
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<tr>
<td>Left 16 (15)</td>
<td>14 (10)</td>
<td>0.024</td>
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<tr>
<td>Right 26 (15)</td>
<td>14 (10)</td>
<td>0.38</td>
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<tr>
<td>Nectosigmoid</td>
<td>13 (10)</td>
<td>0.68</td>
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These results demonstrate that constipation following childbirth or hysterectomy results in a left sided colonic dysmotility with sparing of the right colon. This distinct group of patients could be suitably treated by segmental resection where surgery is being considered.

OUTCOME AFTER ANTERIOR OBSTETRIC SPHINCTER REPAIR IS RELATED TO EXTERNAL SPHINCTER FUNCTION AND ULTRASOUND APPEARANCE

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St Mark's Hospital, London, UK.

Persistent incontinence after primary obstetric repair is associated with a defect on anal ultrasound. We have examined the physiological and ultrasound correlates of a good or poor clinical outcome after secondary repair.

Methods: 26 patients (median age 41, range 26-67) with faecal incontinence after third degree obstetric tear were studied by manometry and anal ultrasound (US) before and after secondary repair.

Results: All 26 had an external anal sphincter (EAS) and 17 also had an internal anal sphincter (IAS) defect on ultrasound, and defects were confirmed at operation. After surgery 18 had improved continence and 8 did not. Improved continence was associated with improved squeeze pressure (post-op squeeze: 20 v 47 cm H2O, p<0.04) and restoration of EAS ring on US (intact ring: 2/8 v 15/18, p<0.04). Pre-op IAS defect did not predict outcome (p=0.1, F exact test). Ultrasound improvement correlated with improved squeeze pressure. Pre-op IAS defect did not predict outcome (p<0.01, F exact test) and was still present in 15 post-op.

Conclusion: A successful sphincter repair is associated with improved external sphincter morphology and function. In failed cases after sphincter repair it may be useful to reinvestigate patients with anorectal manometry and ultrasound.

SCINTIGRAPHIC DEFaecOGRAPHY: THE CLINICIAN'S CHOICE.

R Hutchinson, A Mostafa*, K I Deen, L K Harding* & D Kumar

Department of Surgery, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2TN & Department of Physics & Nuclear Medicine, Dudley Road Hospital, Birmingham, B18 7QH.

To compare a scintigraphic technique of assessing anorectal dynamics with conventional imaging videoprontography (VPG), 60 patients were evaluated using both techniques. Scintigraphic defaecography involves gamma camera imaging while subjects evacuate a 99m-Tc-labelled artificial stool. VPG was performed in the usual way.

Rectal evacuation, anorectal angle, pelvic floor descent, and presence or absence of rectoceles, mucosal prolapse or intussusception were compared. Scintigraphic defaecography provided quantitative information on the rate of rectal evacuation whereas VPG provided only estimates of percentage evacuation. There was agreement between the two methods in the measurement of anorectal angle and pelvic floor descent. VPG showed more small rectoceles, mucosal prolapses and intussusceptions, but these abnormalities were of doubtful clinical relevance. The functional impact of clinically important rectoceles and prolapses were quantified by scintigraphic defaecography.

Furthermore, the low radiation dose of scintigraphic defaecography (1.3 mSv versus 5.5 mSv for VPG) leads us to conclude that it is the investigation of choice for quantitative assessment of anorectal function.
ANAL SPHINCTER DAMAGE OCCURS IN 80% OF FORCEPS BUT ONLY 24% OF VACUUM DELIVERIES; A MAJOR DETERMINANT FOR THE DEVELOPMENT OF Fecal INCONTINENCE.
Sultan AH, Kema MA, Hudson CW, Bartram CI.
St Mark’s, St Bartholomew’s Hospital, London, UK.

In a previous prospective study (Gastroenterology 1992;102(4):A525) 35 percent of first vaginal deliveries developed occult anal sphincter defects. Defects were more likely to occur with a forceps delivery (31% of those delivered by forceps) than with a vacuum delivery (17%).

METHODS: Patients had an unassisted or forceps delivery (20 previous forceps and 17 vacuum delivery) had anal endosonography (Bruel & Kjaer 7 MHz rotating probe), anal manometry (Styrgas-air 16 and microballoon), and pudendal nerve terminal motor latency (FNTML) measurements performed 1 year after delivery. Patients with unavoidable forceps (controls) who had unassisted delivery had the same investigations.

RESULTS: Ten out of 26 (38%) forceps, 2 out of 17 (12%) vacuum, and 2 out of 47 (4%) controls had unassisted delivery, but there were no significant differences.

CONCLUSIONS: Forceps, but not vacuum delivery, is associated with a high incidence of defaecatory symptoms, prolapse, and functional changes. All other obstetric factors being equal, the vacuum extractor should be the instrument of choice when assisted delivery is required.

Budesonide versus prednisolone enema in active distal ulcerative colitis. A comparative eight week study.

In a multicentre, controlled trial, the topically active glucocorticosteroid budesonide, 2 mg/100 ml (Entocort®), was evaluated versus a prednisolone disodium phosphate enema 25 mg/100 ml for the treatment of distal ulcerative colitis.

Patients: 100 patients with active ulcerative colitis not reaching beyond the splenic flexure as determined by endoscopy were included in the study. Mean duration of disease was 6.9 years, and 41 patients were female.

Study design: The study was designed as a randomized, group-comparator investigator blind trial. The investigational drugs were administered at bedtime for up to 8 weeks. The patients were followed as out-patients with visits after 2, 4, and 8 weeks. Therapeutical efficacy was determined by changes in endoscopic and histological scores as well as by registration of symptoms. Patients achieving endoscopic remission after 4 weeks were not treated further. Morning plasma cortisol and S-osteocalcin were measured at each visit.

Results: 55 patients were randomized to prednisolone treatment and 45 to budesonide. Both treatment groups improved significantly during the course of the study but there was no statistically significant difference between the groups at 2, 4 or 8 weeks in terms of endoscopic or histological grading. A lower remission rate was endoscopically achieved after four weeks, and a further 24 at 8 weeks. Mean plasma cortisol was unchanged in the budesonide group, whereas it fell by around 50% in the prednisolone group (p < 0.01) at 2, 4 and 8 weeks. After 8 weeks there was a greater decrease of S-osteocalcin in the prednisolone group (p < 0.05) compared to budesonide, indicating that budesonide may have less impact on bone turnover than conventional glucocorticosteroids. Side-effects were mild and rare in both groups.

Conclusions: Budesonide enema is as efficacious as a conventional steroid enema for the treatment of active distal ulcerative colitis. As a prolongation of the treatment period increases the remission rate, budesonide is preferable to prednisolone because it does not suppress plasma cortisol.
Liver T163–T178


TACE appears to be a useful approach to the treatment of unresectable HCC in cirrhosis. Within 269 pts with HCC observed in our unit in the last 4 years, 52 (19%) were eligible for TACE as single treatment, having tumours with a large or multifocal, no metastasis or portal thrombosis, and a good hepatic function (Child–Pugh risk A/B). Each pt received at least 4 courses of TACE, with 20 mg of Adriamycin suspended in iodized oil (Lipiodol), with subsequent Gel-foam particles embolization in almost all the cases. Tumor size was evaluated by CT-scan after each course. One, 2 and 3 yrs general survivals were respectively 68%, 50% and 35%; pts with lower liver involvement and good liver function (Okuda stage I) had a longer survival. The respective 1, 2 and 3 yrs survival rates were: Okuda I = 70%, II = 42%, III = 22% (p < 0.05). No TACE-related mortality was observed. Transient pain, fever and increase in transaminases were the most frequent side effects; 1 pt (2%) developed a major complication (hepatic abscess), treated by US-guided percutaneous drainage. In 3 pts (6%) a previously undescribed side effect regarding glucose metabolism was observed; 1 pt experienced, 2 days after TACE, diabetic hyperosmotic coma, the other 2 severe hyperglycaemia on the fourth day (without hyperamylasemia or other sign of pancreatic damage), requiring high doses of insulin. The first pt and one of the latter 2 were affected by type II diabetes. In summary, we confirm that TACE is useful and safe in treating unresectable HCC. However, glucose levels must be accurately monitored within the first 5 days from treatment.

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

K C Tan, R D Heaton, V Vougas, N Rela, E Gane, J McPeake, J Wendum and R Williams

King’s College Hospital, London

When orthotopic liver transplantation (OLT) was first considered for patients with hepatocellular carcinoma (HCC) the indications were those tumours deemed unresectable by conventional means. These were usually large tumours associated with decompenasing cirrhosis. Thus it was not surprising that until recently OLT for HCC had been beset with high recurrence rates and poor results.

From past experience at King’s we made a determined effort to transplant only cirrhotic patients with HCC < 6 cm in size. Between October 1989 to December 1991 20 such patients were transplanted. They were followed until December 1992, a median follow up of 30 months and a minimal follow up of 12 months.

The aetiology were HBV in 8, HCV in 4, Alcohol in 4 and one each of alpha-1-antitrypsin deficiency and cryptogenic cirrhosis. Seventeen patients were in Child–Pugh grade B or C, only 3 were grade A. The size of the tumours were <6 cm in 12 patients, 6–6 cm in 6 and >6 cm in 2.

Two patients with recurrent tumours died. Three patients died of septica, 2 of recurrent hepatitis B and 1 in the immediate post-operative period of cardiac tamponade. Twelve (60%) are alive at least one year since their transplant with a median follow up of 30 months.

OLT is certainly indicated in carefully selected cirrhotic patients with small HCC.

REDUCTION OF LIVER TUMOUR GROWTH AND BLOOD FLOW BY OCTREOTIDE. N. Davies, H. Kyannon, J. Yates, S. A. Jenkins & B. A. Taylor. Department of Surgery, Royal Liverpool University Hospital, Liverpool U.K.

Octreotide inhibits the growth of atypical liver tumour in rats.

The aim of this study was to investigate the effects of octreotide on the growth of and blood flow to experimental liver metastases derived from a colon adenocarcinoma.

A colon adenocarcinoma cell line (WB2054M) syngeneic to F1 hybrid rats was used to induce liver tumour. 4x10⁵ cells were injected into the portal vein of 36 F1 rats. 12 rats were treated with octreotide (25g bd) for 4 weeks and 12 treated with saline as a control. At 4 weeks the rats were killed and the Percentage hepatic replacement by tumour was calculated. In the remaining group of 12 rats with liver tumours, tumour blood flow was determined before and after an intravenous infusion of octreotide (0.05 ug/min for 10 minutes) using a dual radio labelled microsphere technique.

There was a significant reduction (Mann Whitney) in the percentage hepatic replacement in the octreotide treated rats, median 1.3% (range 0.64–7.9%), compared to controls 43.9% (36.1–52.2%). There was also a significant reduction in tumour blood flow (ml/min/g) following octreotide infusion; pre 0.37 (0.1–0.97), post infusion 0.14 (0.04–0.45).

The results of this study indicate that octreotide inhibits the growth of hepatic tumour derived from a colon adenocarcinoma. Furthermore, octreotide reduced tumour blood flow, suggesting that this may, at least in part, be its mechanism of action in inhibiting growth.

SYSTEMIC HAEMODYNAMIC EFFECTS OF INTRAVENOUS OCTREOTIDE IN PATIENTS WITH CIRRHOSIS.

McCormick PA, Chin J, Greenslade I, Karatapanis S, Dick R, McIntyre N, Burroughs AK. University Departments of Medicine and Radiology. The Royal Free Hospital School of Medicine London UK.

Octreotide is believed to reduce splanchnic and variceal blood flow with minimal effects on the systemic circulation in cirrhotic patients with portal hypertension. However we noticed significant bradycardia in some patients immediately following bolus doses of octreotide. We therefore studied 52 patients who were having right heart catheterisation prior to liver transplant. 32 received a 25ug bolus and 20 an infusion of 50ug/hr of octreotide/placebo.

Immediately after the bolus dose of octreotide there were significant reductions in pulse rate (77 ± 12 vs 64 ± 11 bpm: p<0.01) and cardiac output (9.2 ± 3.8 vs 7.9 ± 3.0 L/min: p<0.01 and significant increases in mean arterial pressure (81.4 ± 10.6 vs 87.1 ± 12.6 mmHg: p<0.05), mean pulmonary artery pressure (9.1 ± 3.8 vs 16.6 ± 5.9 mmHg: p<0.01), right atrial pressure (4.0 ± 3 vs 6.6 ± 4 mmHg: p<0.01), right ventricular pressure (7.1 ± 2.3 vs 12.5 ± 5.3 mmHg: p<0.01), pulmonary capillary wedge pressure (4.7 ± 3 vs 11.2 ± 5.5 mmHg: p<0.01), systemic vascular resistance and pulmonary vascular resistance 30 minutes after the start of the infusion there was a significant decrease in pulse rate (78 ± 3 vs 73 ± 4: p<0.05) and significant increases in mean right atrial pressure (3.9 ± 0.9 vs 5.5 ± 1.1 mmHg: p<0.01), right ventricular pressure (12 ± 1.2 vs 14.6 ± 1.0 mmHg: p<0.05) pulmonary artery pressure (14.6 ± 1.4 vs 18.2 ± 1.5 mmHg: p<0.01) and pulmonary capillary wedge pressure (9.2 ± 1.3 vs 12.7 ± 1.1 mmHg: p<0.01).

This study suggests that octreotide has significant effects on the systemic circulation in patients with cirrhosis and these effects appear to be more marked following bolus doses.
THE EFFECT OF INTRAVENOUS N-ACETYL-CYSTEINE ON CARDIAC OUTPUT AND OXYGEN UTILISATION IN CIRRHOSIS

A L Jones, P C Hayes
Department of Medicine, Royal Infirmary of Edinburgh.

Previous work suggests N-acetylcysteine improves cardiac output and tissue oxygen use in fulminant hepatic failure, but its action in cirrhosis is unknown.

We studied 5 men and 2 women with alcoholic cirrhosis (4 A's, 2 B, 1 C child's grading) of mean age 65; range 57-72 years.

Pulmonary and liver arterial and portal venous side pressures were taken for oxygen saturation and pH2 estimation. Cardiac output was determined by the thermodilution method. N-acetylcysteine was given at 150 mg/kg for 15 minutes followed by 50 mg/kg for 15 minutes and resulted in an increase in mean oxygen delivery from 639 to 730 ml/min/m2 (p = 0.01, SD = 47.5) due to an increase in cardiac index from 3.27 to 3.83 L/min/m2 (p = 0.02, SD = 0.38). Mean arterial blood pressure did not change significantly (p > 0.5).

Mean oxygen consumption did not rise after N-acetylcysteine (244 ml/min/m2 to 201 ml/min/m2; 0.1 < p < 0.5, SD = 106). There was a rise in mean mixed venous oxygen saturation from 68.4% to 73.1% but this failed to achieve statistical significance (p = 0.2, SD = 14.6).

The difference between the action of N-acetylcysteine in cirrhosis and hepatic failure may occur because cirrhotic patients have established pulmonary shunts and N-acetylcysteine may be acting as a vasodilator to increase pulmonary shunting.

USE OF AQUEOUS CREAM IN THE TREATMENT OF PRURITUS IN PATIENTS WITH LIVER DISEASE. C. Ronayne, G. Robertson and G.P. Grey, Institute of Liver Studies, King's College Hospital, London SE5 9RS.

Pruritus in liver disease, especially primary biliary cirrhosis (PBC), is common, leading to impairment of quality of life and depression. Although many drugs may be used to control pruritus they are not always effective and side effects are common. There have been no previous studies of aqueous cream in the management of pruritus.

Fifteen patients with PBC and pruritus were studied. They washed with their normal soap for 2 weeks followed by aqueous cream for 3 weeks. During this period they monitored their level of pruritus both during the day and at night, using a visual analogue scale, range 1-8.

Washing with aqueous cream resulted in a significant improvement in pruritus both at night and during the day (Table).

<table>
<thead>
<tr>
<th></th>
<th>DAY</th>
<th>NIGHT</th>
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<tr>
<td>VAS Median</td>
<td>5.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Range</td>
<td>1-8</td>
<td>1-8</td>
</tr>
<tr>
<td>p</td>
<td>0.015</td>
<td>0.038</td>
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</table>

Sixty-seven per cent of patients felt that the itching was less troublesome when using the cream. Thirty-three per cent felt that it was unchanged. No patients felt that the cream had worsened their pruritus, and no side effects were reported.

We conclude that aqueous cream is an effective, safe and inexpensive method of controlling pruritus in patients with liver disease.

SUPERIOR STAGING OF LIVER TUMOURS BY LAPAROSCOPY AND LAPAROSCOPIC ULTRASONOGRAPHY

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Careful patient selection is crucial if "curative" resection of focal liver neoplasms is to be worthwhile. Pre-operative staging is often suboptimal using conventional investigations, with high negative laparoscopy rates due to unsuspected dissemination. Using a 7.5MHz linear array laparoscopic ultrasound (LapUS) probe (Aloka, KeyMed, UK), we have prospectively evaluated diagnostic laparoscopy (DL) and LapUS in the management of 42 consecutive patients (24 female; median age 57 years) referred with presumed hepatic malignancy and in whom available radiological investigations indicated resectability. Assessment was towards curative resection in 59% and palliative resection in 3 patients.

<table>
<thead>
<tr>
<th></th>
<th>DL (%)</th>
<th>LapUS (%)</th>
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<tr>
<td>Successful Procedures</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Failed Procedures</td>
<td>2 (5)</td>
<td>2</td>
</tr>
<tr>
<td>Not attempted</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Liver Tumour Visualised</td>
<td>26 (65)</td>
<td>33 (94)</td>
</tr>
<tr>
<td>Irresectable Disease:</td>
<td>16 (40)</td>
<td>17 (49)</td>
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<tr>
<td>Peritoneal Dissemination</td>
<td>15 (38)</td>
<td></td>
</tr>
<tr>
<td>Multifocal/Bilobar Liver Disease</td>
<td>7 (18)</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Hepatic/Portal Venous Involvement</td>
<td>-</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Bilar Lymphadenopathy</td>
<td>-</td>
<td>4 (11)</td>
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</table>

Unnecessary laparoscopy was averted in 23 patients (50%), in six of whom irreversible disease was defined by LapUS but not DL. Liver resection was obliterated by further staging investigations in 5 patients. Ten of 12 patients laparoscopically proceeded to hepatic resection. Absence of liver tumour was confirmed in one case, and right hemi-hepatectomy performed in another with bilar disease. Laparoscopic ultrasonography complements existing investigations in malignancy patient selection for liver resection, can modify the planned surgical approach, and may in future replace conventional staging investigations.

NURSES IN A GENERAL ADULT HOSPITAL ARE ALSO AT INCREASED RISK OF HEPATITIS A INFECTION. F. Rejon, S. Ablouchi, B. O’Farrell, A. Shatollah, M.G. Courtney, J.F. Fielding. Dept. of Medicine and Gastroenterology, Royal College of Surgeons in Ireland and Beaumont Hospital, Dublin and The National Virus Reference Laboratory*, Dublin, Ireland.

Hepatitis A virus (HAV) infection is decreasing in incidence worldwide but infection in adulthood carries a greater morbidity and mortality. It is known that nurses in paediatric hospitals have a higher risk of contracting Hepatitis A.

The purpose of this study was to determine if nurses working in a general adult hospital are at increased risk of contracting HAV infection.

Methods: Serum was obtained from 215 staff nurses and 68 staff nurses working in a general hospital and tested for anti HAV total IgG antibody using an ELISA competitive assay technique. Crude prevalence rates for immunity were compared between the student and staff nurses as were age matched prevalence rates. The differences between the rates were tested for significance using x2 analysis.

Results: 37 (17%) of the 215 student nurses were immune as were 32 (46%) of the 69 staff nurses (x2 = 24.16, p < 0.001). In addition 7 (16%) of the 44 age matched student nurses were immune as were 15 (38%) of the 40 age matched staff nurses (x2 = 4.4, p < 0.05). The differences in seropositivity were not related to differences in travel or number of children as these factors were equal in both groups.

Conclusions: The significant increase in immunity against HAV infection among staff nurses compared to student nurses working in the same hospital suggest that contracting HAV infection is a significant occupational hazard. This may necessitate the institution of a HAV vaccination programme for staff nurses in addition to the existing programme against Hepatitis B.

In the first twelve months of screening for anti HCV the North Western RCT tested 129967 donations using a second generation ELISA (Abbott) and 328 donations were repeatedly reactive (RR).

Of 246 donors referred for confirmation with a RIBA-2 assay (Ortho) 88 (35.8%) were negative, 93 (37.8%) indeterminate and 65 (26.4%) positive. All RIBA-2 positive donors tested for HCV RNA by PCR were confirmed positive, 53 (43 male) confirmed positive donors, age range 19-60 (mean 33.8), have been counselled. Intravenous drug abuse was a risk factor in 29 (67.8%) and was the sole risk factor in 5. Other possible, but unproven risk factors in 19 donors included tattooing, partner with a history if IVDA or transfusion and work in high risk areas.

All donors were asymptomatic, 20 (37.8%) had normal transaminases (range of the others 51-291 IU/L) and alcohol consumption exceeding 40 units per week was reported in 13 (24.5%) cases. 10 (18.9%) donors were positive for anti HB core, 9 (15.1%) for anti Hbs but none for HBsAg.

Thus far 39 donors have consented to liver biopsy, 21 (53.8%) of whom had elevated ALT. No biopsy was entirely normal. 14 (35.9%) showed CHIN of varying degree, 24 (61.5%) CPH or CLH and 1 demonstrated steatosis. This data confirms the high prevalence of established liver disease and viraemia in asymptomatic blood donors with antibodies to HCV, often with normal liver function tests. With the advent of interferon as treatment in chronic HCV infection, this suggests that all individuals with confirmed HCV antibodies should be offered liver biopsy.

MORPHOMETRIC IMAGE ANALYSIS AND EOSINOPHIL COUNTS IN HUMAN LIVER ALLOGRAFTS

Bhaskar Shri Surve2, Booth JD, Rolles K, Dhillon AP, Burroughs AK, Hepato-biliary and Liver Transplantation Unit, The Royal Free Hampstead NHS Trust, Hampstead, LONDON NW3

Pathologic evaluation of liver allografts is the gold standard for diagnosis of acute cellular rejection. Despite this, scoring the severity of rejection and distinguishing it from other infections is not easy. Only 1 group has evaluated biopsies morphometrically and also suggested that eosinophils are a specific diagnostic feature. We quantitated eosinophil counts in 80 biopsies (26 patients) and for 14 patients used morphometric image analysis (microcomputer with a video processing card and chromatic image analysis software) measuring the cross sectional area, the cell density, in each portal tract, in 5 day protocol liver biopsies. Rejection was diagnosed by pathological evaluation confirmed with clinical and biochemical graft dysfunction graded histologically into mild or moderate to severe. The control group was 5 patients with CMV infection and 7 biopsies in whom the cause of the liver dysfunction was obscure. The mean measured cross-sectional area in the 'mild' rejection group was significantly less 65612 µ² versus 12324068 µ² in the moderate-severe rejection group (p<0.001). The mean cell count was significantly lower 150 per portal tract (mild rejection) versus 522 (moderate-severe rejection) (p<0.001). The data for the 2 groups fell in between the two groups. The eosinophil count increased with severity of rejection being 1:3 per portal tract (mild rejection) versus 6:16 (moderate rejection), 20:180 (severe rejection) and zero in the control group. The eosinophil count fell markedly following treatment of rejection. We conclude that morphometric image analysis can be used to quantify acute cellular rejection and that the eosinophil count within portal tracts appears to be specific for the diagnosis of acute cellular rejection, and also parallels severity and response to treatment. These findings provide an essential requirement for the assessment of new immunosuppressive regimes.

LIVER TRANSPLANTATION AND PRIMARY LIVER TUMOURS

T Kurravussi B, Davidson S, Bhattacharya A, Burroughs AK, Rolles K, Royal Free Hospital and Medical School, London.

The value of orthotopic liver transplantation (OLT) in patients with primary liver cancers is controversial. We therefore examined the outcome of patients undergoing OLT for unresectable liver tumours (group 1), cirrhosis with known primary cancer (Group 2) and cirrhosis with incidental tumours on histology (Group 3).

Of 148 patients undergoing OLT over a 4 year period 23 (16M, 7F, median age 50 years (range 16-33)) were transplanted in the presence of tumour. Group 1 (n=28 OLT for hepatocellular carcinoma (HCC) 2, fibrolamellar HCC 2, cholangiocarcinoma (CCA) 1, recurrent biliary cystadenocarcinoma 1, malignant haemangioblastoma 1, Group 2 (n=10) OLT for end stage cirrhosis due to viral hepatitis B (HBV) 5 (C HCV) 3, alcohol 1, primary sclerosing cholangitis 1 and cryogenic cirrhosis 1 with liver tumours diagnosed pre-op (HCC 9, <2cm, 4>2cm) CCA 1). Group 3 (n=6) OLT for cirrhosis due to HBV (2), HCV (1), alcohol (1), primary biliary cirrhosis (1) and autoimmune cirrhosis (1) with incidental tumours (HCC, n=5, 4<2cm, 1>2cm and 1 haemangioma).

In Group 1 (n=7) 5 patients died from recurrent malignant disease and 2 are currently alive (29%). In Group 2 (n=10) there were 2 peri-operative deaths, 1 patient died of metastases and 4 from graft re-infection with HBV. 3 patients are alive and well (30%). In Group 3 (n=6) there was 1 death due to bacterial infection, 1 due to HBV re-infection and 4 patients are alive and well (67%).

Acuarital 6, 12 and 24 months survival were 85.7%, 57.1%, 42.9% for group 1, 87.5%, 75%, 37.5% for group 2 and 83%, 68%, 68% for group 3.

This study would suggest that OLT for unresectable tumours may be inadvisable, survival after OLT for cirrhosis with known tumours is mainly limited by viral re-infection and that incidental tumours do not affect prognosis.
**T175**

**THE EFFECT OF UNSODEXYCHOLIC ACID AND CHENODEXYCHOLIC ACID ON HUMAN HEPATOCYTE AND ERYTHROCYTE MEMBRANES.**

AG Lin*, NA Ahmed, RP Jazrawi, and TC Northfield

Dept. of Medicine, St. George’s Hospital, London, UK.

It has been suggested that cholestasis in primary biliary cirrhosis (PBC) initiated by immunological injury, is perpetuated by membrane damage due to hydrophobic bile acids, and that the therapeutic effect of the hydrophilic bile acid, ursodeoxycholic acid (UDCA) is due to a membrane protective effect.

We tested this hypothesis by examining the effect of tauroconjugates of UDCA, UDCA and of a combination of these on human hepatocyte bile canalicular membrane (BCM) and human erythrocyte membrane (ERM). BCM was prepared from wedge liver biopsies of subjects without liver disease by sucrose gradient ultracentrifugation, and ERM by controlled osmotic lysis and centrifugation. Membranes were incubated with UDCA and ERM alone and in combination at a range of concentrations from 0-10mM. UDCA solubilised more cholesterol and phospholipid from BCM and ERM than UDCA at all given concentrations.

Solubilisation of cholesterol and phospholipid by UDCA reached a plateau of 60% at a bile acid concentration of 3mM whereas the maximal solubilisation by UDCA was 20%, failing to reach a plateau even at a bile acid concentration of 10 mM. When BCM and ERM were incubated with a combination of UDCA and CDCA simultaneously, no protective effect was found. However, the pattern of solubilisation with CDCA was altered to that of UDCA by preincubating these membranes with UDCA. We conclude that CDCA is more damaging to BCM and ERM than UDCA, and that UDCA is able to prevent subsequent membrane damage by CDCA.

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**T176**

**DYNAMIC HEPATOCITOMETRY IN HEALTH AND CHRONIC LIVER DISEASE: COMPARISON OF 95mHIDA WITH 75SeHIDA.**

RP Jazrawi, JS de Carsteker, A Brittain, NFA Joseph, JD Morrow, TC Northfield. Department of Medicine, St. George’s Hospital Medical School, London, UK.

Early (K1) and late (K2) phase plasma disappearance of iv 59SeHIDA (a γ-labeled bile acid) reflect its hepatic uptake and excretion respectively. K1 is a simple test of impaired bile acid hepatocyte uptake and clearance in primary biliary cirrhosis (PBC) which can assess effect of therapy [Clin. Sci. 82: 25P (1992)]. IV 75SeHIDA is not commercially available at a reasonable price and was used to compare plasma-hepatic kinetics of the γ-labeled isotope 95mHIDA with those of 75SeHIDA. Subjects: patients with PBC before and during ursodeoxycholic acid (UDCA) treatment (n=12), other cirrhotics (n=16) and healthy controls (n=12).

Methods: After simultaneous iv 59SeHIDA and 95mHIDA, γ-camera scanning and serial blood sampling were performed for 90 minutes. Measurements: plasma disappearance (K1 and K2 from early and late decline in plasma activity respectively), hepatic uptake, hepatic transit and excretory rate for both 75SeHIDA and 95mHIDA. Results: Correlations were found for above functions between 75SeHIDA and 95mHIDA (K1; r=0.69, p<0.001; K2; r=0.54, p<0.005; uptake; r=0.73, p<0.001; excretory rate; r=0.82, p<0.001 and transit time; r=0.71, p<0.001). All functions were faster for 75SeHIDA than for 95mHIDA (p<0.01). For 95mHIDA, uptake correlated with K1 (r=0.55; p<0.001), and excretion with K2 (r=0.41; p<0.05).

In PBC patients, 95mHIDA excretory rate and K2 were reduced vs controls (p<0.01), and UDCA treatment resulted in improvement in both measures (p<0.05). We conclude that plasma/hepatic kinetics of iv 95mHIDA resemble those of iv 75SeHIDA, but the latter is handled more efficiently and that K2 of 95mHIDA reflects hepatic excretion in PBC and may be useful in assessing the effect of treatment.

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**T177**

**SERIAL HEPATIC 31P MAGNETIC RESONANCE SPECTROSCOPY (MRS) IN ALCOHOLIC LIVER DISEASE.**

Menon DK*, Harris M*, Sargentoni J*, Taylor-Bradford SD*, Cox JH*, Morgan MY*. *The NMR Unit, Hammersmith Hospital, London W12, and †The Academic Dept of Medicine, Royal Free Hospital, London NW3.

Hepatic 31P magnetic resonance spectroscopy (MRS) was undertaken in 22 chronic alcohol abusers of whom 14 of these had either alcoholic steatohepatitis (ASH) and 8 alcoholic cirrhosis (AC). All 22 patients were examined while alcohol consuming, 17 (11AS, 6AC) were reexamined after varying periods of abstinence from alcohol. The reference population comprised 16 healthy volunteers, none of whom consumed >200g alcohol/day. Ratios of phosphomonoesters (PME), inorganic phosphate (Pi) and phosphodiester (PDE), relative to ATP (ATP), were measured in spectra acquired with a 455 pulse and repetition time 5 s.

Active drinking was associated with significant increases in PME/ATP (p<0.001) and PDE/ATP (p<0.001). ATP decrease was not correlated with hepatic steatosis, but was significantly associated with hepatic fibrosis (r=-0.71, p<0.001). A prompt reduction in ATP level was commonly observed with Hples APC/ATP fell to normal or, in the case of decompensated cirrhosis, to subnormal values. These patterns of change were sufficiently distinctive to allow diagnostic separation of the two groups of patients.

The significant increase in ATP observed in PDE/ATP in the hepatic 31P MRS spectrum of individuals chronically abusing alcohol most likely reflects induction of endoplasmic reticulum in hepatocytes, while the reversible component of the PME/ATP elevation probably reflects changes in hepatic lipid, primarily triglyceride.

Change in the rate of ATP phospholipid turnover was not significantly associated with either liver steatosis or fibrosis. ATP reduction was associated with an increase in relative PDE content and subsequent decrease in relative PME content. In the patients with steatosis ATP elevation was particularly significant in both the patients with cirrhosis (p<0.04). In the patients with steatosis, absence of these was associated with a prompt (1-7 days) reduction in PME/ATP, while the PDE/ATP remained elevated for up to 28 days. In contrast, in the patients with cirrhosis, absence of alcohol was associated with little or no reduction in PME/ATP, but a prompt reduction in PDE/ATP fell to normal or, in the case of decompensated cirrhosis, to subnormal values. These patterns of change were sufficiently distinctive to allow diagnostic separation of these two groups of patients.

At present, a reliable immunohistochemical technique to visualise hepatitis C virus (HCV) in liver biopsies is lacking. HCV possesses double stranded RNA (ds-RNA). After raising a polyclonal antibody against ds-RNA in the guinea pig, we stained immunohistochemically paraffin sections of routinely formalin fixed and processed liver biopsies of a total of 106 patients employing the streptavidin method. Identically treated parallel sections but omitting the primary antibody served as negative controls.

There were 56 patients with chronic liver disease and 50 patients with hepatitis C. HCV was detected in 30% of liver biopsies. The specificity of the antibody was demonstrated in patients with acute viral hepatitis (A1V) and chronic hepatitis B with persistent antigenemia (A1V/CHB). The antibody was not reactive with HCV RNA in ds-RNA negative serum and plasma. The antibody was not strongly reactive with ds-RNA positive than with its negative.
Endoscopy T179-T190

WHAT MAKES COLONOSCOPY DIFFICULT?

P.P. Saunders, P.A. Martin, C.D. Williams
St Marks Hospital, City Road, London, E1 1Bp, U.K.

Though colonoscopy is now widely recognised as the investigation of choice for many colorectal disorders it remains a technically demanding procedure in certain patients. In this study 500 consecutive colonoscopies performed by one endoscopist (C.D.W.) were assessed prospectively and difficult cases identified. For the purposes of the study colonoscopy was used to describe loop configuration whenever significant difficulty was encountered during insertion.

In 80% (400) of the 500 examinations the intubation was considered difficult (40 female, 365 male patients). Sixty-five of the 80 difficult procedures were due to recurrent looping of the colonoscope: fluoroscopy showed that 13 patients developed a reversed splenic flexure loop, while in 10 patients the distal tip was not seen and in the remaining 13 cases the distal tip was seen but failed to progress. In 13 patients a combination of reverse sigmoid, reverse colon and colonoscope had failed to progress and in other cases the colonoscope had made progress through the sigmoid, but failed to progress further. In 10 of these cases an overtube device was used successfully to prevent recurrent looping in 9 patients.

The cause of difficulty in the remaining 15 cases was a fixed sigmoid colon secondary to diverticular adhesions in 6 patients and previous surgery in 9 patients (8 female, 1 male). In 5 of these patients the paediatric (10mm) colonoscope was successful in passing the sigmoid when the adult scope had failed. In 4 patients fixation of the sigmoid colon lead to failure of the procedure, though in two of these cases the sigmoid was only partially obstructed. In all difficult cases the mean time taken for intubation was 24 minutes (max. 60 mins.) and the mean sedation used was propofol 40mg i.v. and diazepam 4mg i.v. (max. propofol 100mg, diazepam 10 mg).

We conclude from this study that the majority of difficulties at colonoscopy are unpredictable and due to recurrent looping of the colonoscope in a mobile left colon. When persistent looping occurs it can not be accurately assessed (even by an experienced endoscopist) without external imaging and therefore despite its many disadvantages fluoroscopy remains a useful aid in the difficult case. A fixed sigmoid colon was the only reason for clinical failure in this study and in such cases a change to the more flexible paediatric colonoscope may be helpful.

T180

A SIMPLE METHOD FOR MANAGEMENT OF GALLSTONE BASKET IMPACTION AT ERCP.-Benzon ML, van Someren RMS, Amley CC, Glynn MJ, Department of Gastroenterology, The Royal London Hospital, London E1 1BB.

During ERCP, impaction of a gallstone-containing basket in a sphincterotomy which is too small to allow passage of the stone is a complication usually resolved by surgery. We have developed a simple procedure for crushing such an impacted stone which can be performed immediately without resorting to surgery. The initial step is to separate the plastic handle from the basket wire using a stout pair of piers. If a 2.8mm cholangiographic basket tip is at all impacted it is then completely withdrawn, together with the polyurethane sheet enclosing the basket wire. This sheath is fed through the operating channel of a 3.6mm duodenoscope, and the new duodenoscope retrogradely fed over the basket wire until the tip lies against the impacted stone. Use of the sheath is necessary to allow the rigid proximal end of the basket wire to negotiate the y-junction of the operating channel. The basket sheath is then discarded. If a 3.6mm duodenoscope is already in use, the sheath is discarded over the wire, leaving the duodenoscope still in place. A 12F biliary dilator, which has considerably more resistance to compressive forces than the sheath, is placed against the impacted basket and stone, under direct vision, by sliding it over the basket wire. Using a combination of traction on the basket wire and pushing the dilator, the basket is drawn into the distal end of the dilator. The stone is either crushed, or else released after fracture of one of the wire strands of the basket.

We performed 1354 ERCPs in the 36 months until December 1992, out of which 464 were for extraction of gallstones. During this period, 6 cases of gallstone impaction occurred. Prior to devising this simple technique, one was treated by laparotomy and one by a later ERCP, using a mechanical lithotripter over the impacted basket. The last 4 cases were successfully managed at the time of initial ERCP using our technique. The time taken to perform this varied, from 30 to 45 minutes. In each case a balloon occlusion cholangiogram demonstrated no evidence of extra-biliary leak of contrast.

It is obviously preferable to avoid the impaction of a gallstone-containing basket occurring at all. However, methods for assessing the size of a sphincterotomy and tissue elasticity are impractical. Therefore, it is likely that this complication will continue to arise, but can now be managed in a straightforward and safe manner.

T181

INVESTIGATING PATIENTS WITH UPPER GASTROINTESTINAL SYMPTOMS: OUTPATIENTS OR ENDOSCOPY DIRECT? A RANDOMISED CROSS OVER TRIAL

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General practitioners like direct access endoscopy, but is it used appropriately, is the final diagnosis speeded or slowed by endoscopy, how many patients need more tests?

GPs given referral guidelines requested direct access endoscopy for 400 patients. After randomisation, 197 were reviewed in outpatients before endoscopy, 203, endoscopy first, then assessed in outpatients without knowledge of the endoscopic findings to detect any other medical problems.

380 (95%) referrals fulfilled the guidelines; 333 patients completed the study and referral was thought appropriate in 303 (91%). Inappropriate referral might have caused serious harm in 3 and delayed diagnosis in 23 (21 serious). Mean wait for outpatients first was 53 days; endoscopy first 24 days (p=0.0001). The final diagnosis was made at endoscopy in 264 patients (79%). 86 endoscopies were normal; 80 of these and 25 with trivial abnormalities were finally considered functional. 77% of the 80 patients were asymptomatic 1 to 3 months after the reassurance of a normal test. 17 patients had disease outside the GI tract, 22 other upper GI diseases, 5 lower GI disease. Direct access endoscopy is quick and valuable in 79% of patients, but hazardous in 1%; 21% require further investigation. Family doctors should assess all patients clinically before and after direct access endoscopy. Efforts must be made to detect the small number of patients potentially at risk from endoscopy.

T182

ACUTE GASTRO-INTESTINAL HAEMORRHAGE IN ANTICOAGULATED PATIENTS; DIAGNOSIS AND RESPONSE TO ENDOSCOPIC THERAPY. C-F. Choudhuri, C. Bethnal, K.R. Palmer, GI Unit, Western General Hospital, Edinburgh.

It is known that most patients who present with upper gastrointestinal haemorrhage whilst taking oral anticoagulants bleed from underlying ulcer disease. Whether their response to endoscopic therapy is known. A study of 605 patients undergoing emergent endoscopy for acute upper gastrointestinal bleeding were receiving Fafarin therapy; 8 were also taking NSAIDs. Although 7 patients had previously documented peptic ulcer, only 5 patients had recent dyspeptic symptoms.

Endoscopy, performed within 12 hours of admission after correction of the International Normalized Ratio (INR) to 2-2.5, revealed a bleeding site in 33 patients (88%). Peptic ulcer was found in 21 patients; 19 of these had major stigmata of recent haemorrhage and were treated by endoscopic injection or the heater probe. Endoscopic therapy was uncomplicated and permanent haemostasis was achieved in all but one patient after one or two sessions. In 7 patients, no diagnosis was made despite gastroscopy and colonoscopy, and none of these patients relapsed. No relationship was found between the degree or duration of anticoagulatation (INR) and the likelihood of finding an underlying lesion. Warfarin therapy was continued long term in 20 patients and no further bleeding occurred over an 8 month median follow-up period.

Early endoscopy is mandatory in anticoagulated patients presenting with upper gastrointestinal haemorrhage. Endoscopic therapy is safe and effective in appropriate, high risk subjects and long term use anticoagulants can then be safely reinstated.
THE OUTCOME OF MAJOR PEPTIC ULCER HAEMORRAGE IS BEST IN PATIENTS TAKING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS). C. J. Choudari, K.-R. Palmez, GI Unit, Western General Hospital, Edinburgh.

We anticipated that the prognosis of patients who present with major peptic ulcer haemorrhage who are taking NSAIDs (excluding aspirin) may be relatively poor. Such patients tend to be elderly, they commonly have multi-system diseases and NSAIDs inhibit platelet function.

Forty one of 114 patients admitted consecutively because of serious peptic ulcer haemorrhage were taking NSAIDs. Those taking NSAIDs were significantly older than those not taking these drugs (mean age 70.3 ± 12 versus 62.4 ± 16.6 years, P < 0.004), more of the NSAID group had cardio-respiratory disease (49% versus 26%) and were shocked on admission (708 versus 55%). All patients had major endoscopic stigmata of haemorrhage; ulcer distribution and range of endoscopic findings (active arterial haemorrhage and protuberant vessel) were similar in the two groups. All patients underwent endoscopic injection therapy, performed by a single endoscopist.

Mean transfusion requirement (3.9 ± 3 versus 4.8 ± 3.3 units), need for emergency surgery (7.3% versus 13.7%) and hospital mortality (2.4% versus 4.4%) were all lower in the NSAID group. Uncontrolled haemorrhage and rebleeding were equally common in both groups.

Although patients who present with peptic ulcer haemorrhage whilst taking NSAIDs tend to be older and commonly have multi-system diseases, their prognosis is better than that of patients who are not taking these drugs.

LIVER BLOODIE BLEEDING TIME: AN UNPREDICTABLE EVENT
J Dillion, K Simpson, P C Hayes
Department of Medicine, Royal Infirmary, Edinburgh, EH3 9YN

Liver biopsy is an essential diagnostic aid, but is associated with a risk of haemorrhage. It is believed that this risk is related to platelet count and prothrombin time. Using laparoscopy under local anaesthesia it is possible to observe directly post biopsy liver bleeding.

We performed laparoscopically guided liver biopsy on 51 consecutive patients (median age 49, 6 females, 19 males) who underwent 60 biopsies (8 patients had more than one biopsy). Post biopsy liver bleeding time was observed and recorded. If it was longer than 10 minutes bleeding was stopped by direct pressure. Patients who had a coagulopathy or a thrombocytopenia considered a contraindication to blind liver biopsy did not have this corrected prophylactically.

Results: Histology: 7 normal, 11 hepatitis, 9 fatty liver, 4 metastatic carcinoma and 20 cirrhosis. The mean platelet count was 253.9 (range 55-1352) and mean prothrombin time ratio was 1.1 (range 0.9-2.1).

The mean liver bleeding time was 4.6 minutes (standard error ± 0.47). Eight patients bled for > 10 min requiring intervention (all had normal PTR and accessible ulcer at attempt). No patient sustained a delayed post biopsy bleed. There was no correlation between liver bleeding time and PTR or platelet count. For the different histological groups intrapatient and interpatient variance was similar. In those patients who had more than one biopsy performed the intrapatient variance was similar to the interpatient variance.

Conclusion: Mild to moderate coagulopathy (PTR < 2.1, platelet count > 55 x10^3 /l) does not appear to be associated with prolonged bleeding following liver biopsy. Equally normality of the coagulation studies did not negate the risk of post liver biopsy bleeding.

ENDOSCOPIC FINDINGS IN ASYMPTOMATIC BLOOD DONORS ACCORDING TO HIGH LEVELS OF IgG, IgA, IgM TO HELICOBACTER PYLORI (HP) AND HIGH LEVELS OF SERUM PEPSEONID (PIG)
1st Medical Clinic, University of Bologna, Departament of Paediatric Gastroenterology & Chemical Analysis, University of Turin, Italy; 2nd Department of Microbiology, The Middlesex Hospital, London, U.K.

We have previously reported an high seroprevalence of IgG, IgA, IgM to HP and PGI in a large asymptomatic blood donors population (24%, 29%; 45%; and 25%, 42%, 23%, 45% and 245/100 respectively).
The total blood donors population have been divided in 8 subgroups according with high levels of IgG (IgG only (n=69); IgG+IgA (n=50); IgA (n=14); IgG+IgM (n=60); IgM+IgG+PGI (n=29); IgG+IgA+IgM (n=61); VIGG+IgA+PGI (n=36) and VIIIgG+IgA+IgM (n=54)). We now report the results in the first seven subgroups. Endoscopy was offered to the first seven consecutive subgroups (n=368). After interviewing (n=324, 88%), 253 (78%) (M:F 137/116; age range 18-85 ; mean 45 yrs) underwent upper gastrointestinal endoscopy. During endoscopy 4 antral biopsies were taken for CP-Test (1), culture (1), microscopy (Giema and Hematoxilin & Eosin staining) (2). Venous blood was collected and IgG to HP was re-assesed.

Results: The endoscopic findings were: 1 gastric cancer, 1 leiomyosarcoma, 39 duodenal ulcers, 14 gastric ulcers, 34 erosive duodenitis, 29 antral erosions, 96 anal gastritis and 39 endoscopically normal. 233 found out of 253 (92%) harbored HP assessed by Giema, CP-TEST and/or culture and high levels of IgG.

Twenty patients (8%) were not colonized by HP assessed by all the four methods. Interestingly in 19 of these 20 the levels of IgG had fallen by the time of endoscopy. No difference was found in the endoscopic findings according to the seven subgroups considered above.

Conclusion: This study is the first time that we have shown the clinical relevance of high levels of IgG only to HP in screening population independently of the association with the others parameters considered above. We confirm in this larger population the surprisingly high prevalence (20%) of undiagnosed peptic ulcers in healthy subjects.
## BOWEL PREPARATION NOT SEDATION INFLUENCES TOLERANCE OF COLONOSCOPY.

CSJ Probert, H Quirk, RA Mountford University Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW.

A prospective study of the determinants of tolerance of colonoscopy was performed between December 1987 and September 1990. 250 patients underwent 281 procedures by a single experienced endoscopist. The patient’s tolerance and preparation were described subjectively as good, acceptable, poor or unknown. The number of men and women was the same. The age range was 7.5 years to 90.2 years (mean 55.9). 115 people were aged 60 years or more. Tolerance did not vary with age (p<0.05). Men and women fared equally well (p=0.05). The dose of midazolam varied with the patient’s age. Most young patients (89%) received at least 1mg, while only 40% of the older patients were given this dose of midazolam (X²=32, p<0.001). 27.8% of older patients were given up to 5mg midazolam only 8.7% of younger patients received this dose (X²=55.4, p<0.001). Tolerance did not differ with the dose of sedation (p<0.05). Thus, a higher dose of midazolam did not necessarily improve tolerance. The majority of patients underwent bowel preparation with Picolax (n=163, 65%), while 61 (24.4%) had polyethylene glycol. The quality of the preparation did not differ with the type of preparation. However, the quality of the bowel preparation influenced the patients’ tolerance of the colonoscopy such that well prepared patients were more tolerant than those who were poorly prepared (X²=20, p<0.001).

Colonoscopy should be aware that bowel preparation, not sedation, determines tolerance.

## RESUSCITATION SKILLS IN ENDOSCOPY STAFF - A CAUSE FOR CONCERN? 

T D Wardle, K J Moriarty, Department of Medicine, Hope Hospital, Salford, M6 8HD, Department of Gastroenterology, Bolton General Hospital, Bolton, BL4 OJR.

All medical and paramedical staff, in particular those in “high risk” areas e.g. the endoscopy unit, should be able to perform basic life support (BLS). We assessed the ability of endoscopy unit staff to perform BLS. Thirty candidates (9 doctors, 21 nurses) were presented with a resuscitation manikin (the patient) and a scenario. They were scored on their assessment and resuscitation skills based on the British Resuscitation Council directives and were re-assessed after practical instruction in BLS.

<table>
<thead>
<tr>
<th>Procedure/Step</th>
<th>Max Score</th>
<th>Pre-Instruction</th>
<th>Post-Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway(A)</td>
<td>4</td>
<td>1</td>
<td>0.7±0.1*</td>
</tr>
<tr>
<td>Management - unobstructed</td>
<td>1</td>
<td>0</td>
<td>0.7±0.1*</td>
</tr>
<tr>
<td>Management - obstructed</td>
<td>3</td>
<td>0</td>
<td>2.4±0.3*</td>
</tr>
<tr>
<td>Breathing(B)</td>
<td>3</td>
<td>1.3±0.8</td>
<td>2.5±0.2*</td>
</tr>
<tr>
<td>Oropharyngeal airway</td>
<td>2</td>
<td>0.8±0.4</td>
<td>1.7±0.1*</td>
</tr>
<tr>
<td>Circulation(C)</td>
<td>2</td>
<td>1.7±0.1</td>
<td>0.9±0.06</td>
</tr>
<tr>
<td>Palpate major pulse</td>
<td>5</td>
<td>2.3±0.1</td>
<td>4.4*</td>
</tr>
<tr>
<td>External Cardiac Compression</td>
<td>1</td>
<td>0.7±0.1</td>
<td>0.9±0.06</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20</td>
<td>6.9±1.9</td>
<td>17.0±1.6</td>
</tr>
</tbody>
</table>

Significantly greater than pre-instruction score (P<0.001). *Significantly greater than pre-instruction score (P<0.001).

No candidates performed BLS adequately. Most (26) started resuscitation without adequate initial assessment and did not progress logically through the ABC sequence. Management of the unobstructed airway and identification of a major pulse were done competently by all candidates. After instruction there was a significant improvement in all of the other skills. In conclusion, BLS skills, although inadequate in all candidates, were rapidly acquired following instruction. All users of endoscopy facilities should be assessed and trained where appropriate in BLS.

## ENDOSCOPIC SPHINCTEROTOMY IN THE YOUNGER PATIENT: SUCCESS AND COMPLICATIONS.

D G Maxton, D E F Tweedle, D P Martin Gastroenterology, University Hospital of North Staffordshire, Stoke on Trent, ST4 7DB.

Older patients with both common bile duct (CBD) and gall-bladder stones can be effectively managed by endoscopic sphincterotomy (ES) and stone extraction without subsequent cholecystectomy. The choice for younger patients now lies between endoscopic stone extraction and interval laparoscopic cholecystectomy or CBD exploration during an open procedure.

Between 1982-92 we performed ES in 117 patients under 55 years (mean age 41.9 years, range 19-55, 92 female: 25 male). In 85 (73%) the indication was retained CBD stones after biliary surgery and in the remainder acute biliary obstruction often combined with poor general medical condition. Successful biliary drainage was achieved in 108 (92%, 96 (82%) requiring only 1 or 2 ERCPs (range 1-6).

Complications occurred in 23: pancreatitis in 10, retroperitoneal perforation in 2 and significant haemorrhage in 10, requiring laparotomy. All recovered apart from 1 other 'high risk' patient who died after surgery for an impacted stone. The overall complication rate was 20%: 27% between 1982-87 but falling to 14% during 1987-92. CBD stones were successfully removed from 4 pregnant women without incident.

We have generally been reluctant to perform ES in younger patients except in a selected group not considered suitable for surgery. CBD stones can usually be successfully extracted endoscopically in younger subjects. Complications, though relatively frequent, are rarely severe and the single death occurred in an especially unfit individual. Complications may be lower in young fit patients being considered for laparoscopic cholecystectomy.

## THROMBIN - AN EFFECTIVE TREATMENT FOR FUNDAL GASTRIC VARICES?

SG Williams, RA Peters, D Westaby Charing Cross Hospital, London W6 8RF

In 20 - 30% of patients with variceal haemorrhage the bleeding point is in the gastric fundus. The treatment of gastric varices is controversial, particularly those within the fundus. Injection sclerotherapy is associated with a high failure rate. Tissue adhesive injection has proven value but is difficult to use and serious complications have been reported.

We have evaluated human thrombin as an alternative injectate in a series of 11 patients, over an 11 month period, with proven gastric variceal bleeding (9 (82%) from large fundal and 2 (18%) from lesser curve varices). 10 (91%) had previously undergone sclerotherapy for oesophageal varices, and 1 (9%) had had ethanolamine injected into a fundal gastric varix.

Thrombin was injected intra-varically in 1ml aliquots of 1,000U/ml to a total of 10 mls. (range 2-10mls.). The patients underwent 20 sessions of thrombin injection at a median of 2 per patient. Treatment was repeated at one to two week intervals until the varices were considered thrombosed or obliterated.

Re-bleeding during the same admission occurred in one patient from a friable gastro-oesophageal junction distant from the treated gastric varix. Late re-bleeding, (follow up 4-11 months, median 7 months), occurred in two patients. One bled from oesophageal varices and the other re-bleed from lesser curve gastric varices during the pre-terminal phase of severe alcoholic hepatitis.

No complications directly related to thrombin injection were documented.

We suggest that thrombin may represent a valuable alternative injectate for the management of gastric varices.
**T191**

**QUANTITATION OF INFLAMMATORY BOWEL DISEASE (IBD) ACTIVITY USING Tc HMPAO SINGLE PHOTON EMISSION COMPUTERISED TOMOGRAPHY (SPECT)**

H J Heldon, A M Masoomi, A Britten, A E A Joseph, I J Maxwell (St George's Hospital Medical School, London).

Tc HMPAO white cell scanning can be reliably used to assess extent of IBD on routine planar images. However, assessment of disease severity by quantification of uptake in bowel is more difficult due to overlapping activity e.g. in bone marrow. SPECT is a technique already being applied to imaging of other organs (heart and brain). It can provide trans-axial images of the abdomen in which uptake of Tc HMPAO in bowel is clearly separated from other structures, particularly the bone marrow.

In order to assess the accuracy of this imaging technique in IBD, Tc HMPAO SPECT was performed in 20 patients with suspected colonic involvement.

Uptake in each of 5 colonic segments (rectum, sigmoid descending, transverse, ascending) was quantified on transaxial images and expressed as a ratio of marrow uptake. Colonoscopy was then performed within 14 days and severity was assessed histologically in the same 5 segments and graded 0-3. Correlation of segment histology score vs segment/marrow uptake ratio was r = 0.92 (p < 0.001). Total bowel/marrow uptake ratio correlated with Crohn’s disease activity index, r = 0.6, p = 0.01.

In conclusion Tc HMPAO SPECT imaging can clearly separate actively affected bowel from other structures and allows accurate disease activity quantification. This non-invasive technique may be useful in objective evaluation of new therapies for IBD.

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**T192**

**ROLE OF CYCLOSPORIN A AS AN INITIAL THERAPY FOR CHILDHOOD CROHN'S DISEASE**

S Micholls, A Dawson, CB Williams, TT MacDonald, JA Walker-Smith

Dept. of Child Health, St. Bartholomew’s Hospital, London, EC1A.

Childhood Crohn’s disease (CD) may cause significant morbidity. T-cell activation is central to CD pathology: as cyclosporin A (CsA) is a powerful inhibitor of such activation in vitro, and has been used in adult CD with encouraging results, it appears to open the prospect of prolonged remission if given early in the course of disease. We therefore studied newly-diagnosed children, plus those relapsing off therapy. CsA or conventional therapy (elemental diet or corticosteroids) was randomly allotted. CsA levels maintained at between 100-150 µg/l. Evaluation was performed initially and at 2 months.

So far 22 children have been enrolled (8 CsA, 14 conventional [1 child on CsA withdrew]). Clinical remission occurred in 5/8 on CsA and 13/14 on conventional therapy. Colonscopic improvement was noted in 3/7 on CsA (none returned to normal) and 8/14 on conventional (1 to normal). Basal GAG improvement was seen in 6/6 on CsA (2 to normal) and 8/14 on conventional treatment (5 to normal). Children with initially normal histology were not re-biopsied.

Median Lloyd-Still index changed from 41.0 to 48.2 on CsA, & from 43.2 to 55.0 on conventional therapy, while CRP fell from 32.0 to 29.5 on CsA, & from 40.8 to 14.5 on conventional therapy.

CsA significantly improved histological appearance without matched improvement in symptoms or disease indices. Whether such histopathological improvement offers the prospect of sustained remission awaits evaluation.

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**T193**

**INDOMETHACIN-INDUCED CAecal DIAPHRAGMS IN A CRONH’S NSAI STUDY**

A. Anthony, A. P. Dhillon, G. Nygard, R. E. Pounder, A. J. Wakefield

Inflammatory Bowel Disease Study Group, Royal Free Hospital School of Medicine, London, UK.

In patients on chronic NSAID therapy, a clinicopathological entity called “diaphragm disease” has been described consisting of gastrointestinal strictures and submucosal fibrosis. We performed a chronic NSAID feeding-study in rats and describe caecal strictures that strongly resemble human “diaphragm disease”. Methods Groups of male Sprague-Dawley rats (n=8/10/group) received indomethacin in a powdered diet at levels of 0.3 and 6mg/kg/day for 6 weeks. At terminal laparotomy, the gastrointestinal tract was arterial perfusion-fixed and examined macroscopically and histologically in an observer-blinded fashion. Results At 6mg/kg/day (n=8), 2 rats died of jejunal perforation within 13 days and 5 others underwent early termination at 17 days because of severe weight loss. At 3mg/kg/day (n=10), all animals survived to 6 weeks with no weight loss. There was dose-dependent formation of both concentric slit-like and broad-based septa arising from the caecal mucosa that showed histological features of submucosal fibrosis and chronic inflammation in 30% and 63% of the 3 and 6mg/kg/day indomethacin-fed animals, respectively. The presence of submucosal chronic vasculitis, endarteritis obliterans and haemosiderin deposition supported the chronic nature of these lesions. The small bowel showed multifocal ulceration in 30% and 100% of the 3 and 6mg/kg/day groups, respectively, while no control animals (n=8) showed any gastrointestinal abnormality. Concluding We describe chronic caecal diaphragms in rats that received long-term diabetic indomethacin. The macroscopic and histological features of these experimental submucosal lesions closely resemble human “diaphragm disease”. This study was funded by Glaxo Group Research Ltd, Ware, UK.

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**T194**

**REDUCTION OF SULPHATED GLYCOSAMINOGLYCANS AND INTESTINAL ALBUMIN LOSS**

SN Murch, TT MacDonald, AD Phillips, M Levin, JA Walker-Smith, P Lionetti, R.J. Klein

Departments of Paediatric Gastroenterology, St. Bartholomew’s Hospital and of Child Health, St. Mary’s Hospital, London.

It is now recognised that the clearance of albumin by bowel is limited by charge-based interactions with sulphated glycosaminoglycans (GAGs), so that loss of GAGs leads to vascular albumin leak or the nephrotic syndrome abnormality. We now present evidence to suggest that a similar mechanism exists within the intestine and that loss or congenital absence of intestinal GAGs may be associated with protein loss.

We have used histochemistry to compare GAG distribution in jejunal biopsies obtained from a normal infant to those taken from a 5 month old infant with similar normal histology but a history of severe life-long intestinal albumin loss, who has required continuous albumin infusion. The affected infant showed patchy loss of GAGs in the subepithelial basal lamina and the complete absence of interstitial GAGs. He had however a normal pattern of interstitial and vascular lamina propria GAGs.

There is also evidence that macrophage-derived cytokines can cause GAG loss. As albumin loss may be severe in inflammatory bowel disease, we have studied intestinal inflammation in 2 groups of CD patients with Crohn’s disease, 6 with ulcerative colitis (UC) and 8 controls. In all disease specimens, there was also marked disruption of submucosal vascular and interstitial GAGs, related to local macrophage density. Both increased vascular leak and decreased basal lamina restriction might contribute to albumin loss during inflammation.
CIRCULATING PLATELETS ARE ACTIVATED IN INFLAMMATORY BOWEL DISEASE (IBD). CE Collins, MR Cahill, MG MacKe, AC Newland, DS Rampton, GI Science Research Unit and Dept of Haematology, Royal London Hospital, London.

Activated platelets play a role in the vascular damage associated with ischaemic heart disease and diabetes. Systemic thromboses may complicate active IBD and recent evidence suggests there is significant intestinal vascular endothelial injury in Crohn’s disease. We tested the hypothesis that platelet activation contributes to the pathogenesis of IBD.

METHODS: We used i) flow cytometry to quantify the platelet surface antigens P-selectin (a specific adhesion receptor for neutrophils released from alpha-granules) and GP53 (a lysosome-derived protein), both of which are expressed on activation, and ii) ELISA to measure beta-thromboglobulin (BTG), a platelet-specific protein discharged from alpha-granules on activation. Disease activity was defined according to the modified Harvey-Bradshaw index.

RESULTS: There was increased expression of surface markers in all IBD groups, and of BTG in active CD and inactive UC. % cells positive for specific fluorescent antibody marker, and serum BTG in IU/ml, are shown as medians (interquartile range):

<table>
<thead>
<tr>
<th>n</th>
<th>P-selectin</th>
<th>GP53</th>
<th>n</th>
<th>BTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>controls</td>
<td>32</td>
<td>1.8 (1.3-3.3)</td>
<td>15</td>
<td>1.0-2.6</td>
</tr>
<tr>
<td>active CD</td>
<td>17</td>
<td>1.5 (1.8-3.3)</td>
<td>25</td>
<td>19-46</td>
</tr>
<tr>
<td>inactive CD</td>
<td>17</td>
<td>4.0 (1.6-10.7)</td>
<td>15</td>
<td>15-25</td>
</tr>
<tr>
<td>active UC</td>
<td>13</td>
<td>1.1 (4.1-13.6)</td>
<td>10</td>
<td>18-25</td>
</tr>
<tr>
<td>inactive UC</td>
<td>13</td>
<td>3.5 (2.3-5.6)</td>
<td>10</td>
<td>17-28</td>
</tr>
</tbody>
</table>

*p<0.05, t*p<0.01 vs healthy controls using Mann-Whitney U.

CONCLUSION: Platelets circulate in an activated state in IBD. This abnormality could contribute to the pathogenesis of IBD by promoting neutrophil adhesion, and by predisposing to thrombosis and inflammation in the vasculature of the bowel wall and elsewhere.

PLATELET ACTIVATION IN INFLAMMATORY BOWEL DISEASE: HD Schaufelberger, MR Uhr, AC Smith, KPH Logan, PC Gordon-Smith, JI Maitzer, Department of Gastroenterology, Central Middlesex Hospital London NW10 7NS and Division of Haematology, St George’s Hospital London SW17 0RE.

Abnormal coagulation is involved in inflammatory bowel disease (IBD). P-selectin (GMP140, CD62), a receptor molecule responsible for neutrophil and monocyte recognition, is uniquely expressed on the surface of activated platelets and vascular endothelial cells. We have investigated the contribution of activated vascular endothelium in the pathogenesis of IBD.

Twenty patients (median age 38y (15-73, range 13 men) with either ulcerative colitis (UC) n=12, 5 active, 7 inactive) or Crohn’s disease (CD n=8, 3 active, 5 inactive) were studied and compared with 9 healthy volunteers (median age 31y (23-40) 4 men). IBD was graded as active/inactive, using the Harvey-Bradshaw classification. Circulating activated platelets in venous whole blood were assessed by their expression of the membrane protein GMP140, measured semiquantitatively by flow cytometry on a random sample of 8,000 platelets from each subject.

The percentage of circulating activated platelets was significantly increased in the IBD group as a whole compared to healthy subjects (18.8%, mean 4.2%, SEM vs 4.3% (1.5%), P<0.001). When considered separately, patients with UC (20.5% (2.5%)) and CD (16.6% (2.2%)) had increased numbers of activated platelets compared to normals, (P<0.001), Patients with active disease, either UC or Crohn’s, did not differ from those with inactive disease. (22.1% (1.5%) vs 16.9% (3.7%), P=0.23). (Independent t-test on absolute values, converted to % for clarity)

Our finding suggest that patients with IBD show a persistent response to haemostatic and/or inflammatory tissue injury but that this does not depend upon disease activity.