Results: The mean age of the patients (65 males; 75 females) was 66 years (range = 27–96). The rate of cannulation of the duct of interest was 127 out of 140 cases (91%), and both endoscopists and radiologist's reports were available in 118 of these.

Abstract 387, Table 1

Categories n (%)

I	II	III	Total (n)
104	11	3	118

Conclusion: The role of radiologists' interpretation of post-procedure ERCP spot films is small but significant. We believe this procedure should continue but be subject to further review.

- Shah RJ, Sweeney JT, Ulrich CD, Martin SP, Somogyi L. ERCP interpretation by radiologists: does it have a role? *Gastrointestinal Endoscopy* 2000;51(4):AB76.

388 THE ROLE OF SPIRAL CT CHOLANGIOGRAPHY IN PATIENTS WITH ABDOMINAL PAIN POST CHOLECYSTECTOMY

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Introduction: Patients (pts) with biliary type abdominal pain post cholecystectomy are often referred to gastroenterologists for ERCP. In view of the recognised risks associated with this procedure, the role of spiral CT cholangiography (sCTC), which has been shown to be highly sensitive for the detection of bile duct filling defects, in addition to ultrasound (US) and liver function tests (lfts), was examined to determine if all requests were appropriate.

Methods: 20 pts (7 male, 13 female, age range 32–83 yrs), in whom ERCP was not thought to be immediately indicated, were referred to sCTC. All had had a cholecystectomy within the last 5 years. No pt was jaundiced. After lfts and US had been performed, all patients had sCTC using i.v. biloscopin, reported by one consultant radiologist. Only pts shown to have biliary stones by sCTC underwent ERCP.

Results: sCTC was successful in 18/20 pts (contract may not be excreted if there is abnormal liver function). 5 pts had biliary stones detected by sCTC (4 with normal calibre bile ducts on US); these were all confirmed at ERCP. 13 pts had a normal sCTC. Only 11 of these pts had had a previous US, each of which was normal. sCTC was normal in the 9 pts with normal lfts. 5 patients with abnormal lfts had a normal sCTC.

Conclusion: sCTC provides high resolution images of the biliary tree in the majority of patients. It is capable of picking up stones even in the presence of a non dilated biliary tree on US. sCTC should be considered in selected patients prior to ERCP and may prevent unnecessary procedures.

Liver Posters: 389–410

389 ORTHOTOPIC LIVER TRANSPLANTATION, PSC, IBD AND COLORECTAL CARCINOMA

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Aim: We reviewed our centre's experience of prevalence of IBD in patients undergoing transplantation for PSC, indication for colectomy and incidence of colorectal carcinoma.

Methods: Patients were identified from a prospectively maintained database then retrospective case note analysis was undertaken.

Results: 936 patients underwent orthotopic liver transplantation between January 1982 & February 1999 and subsequently followed up for >12 months. 105 were transplanted for PSC (with no evidence of cholangiocarcinoma), 78 men and 27 women with a mean age of 45.5 years were followed up for a median of 61 months (range 13–143). Pre-transplant 66 patients (62.9%) were diagnosed with UC

and 4 (3.8%) with Crohns. Post-transplant this rose to 78 (74.3%) with U.C. and 5 (4.8%) with Crohns. Colectomy for non malignant indications: pre-transplant - 9 (2 dysplasia, 7 symptomatic), peri-operatively - 1 for dysplasia, post-operatively - 5 (1 dysplasia, 4 symptomatic). 7 patients, all with UC, developed colorectal adenocarcinoma and 1 caecal lymphoma. Incidence of colorectal adenocarcinoma in patients transplanted for PSC with an intact colon was 7.4% compared with 0.8% for the rest of transplant group ($p < 0.05$) and 12.3% in patients with UC diagnosed prior to transplantation for PSC. Malignancy arose after a median of 4.5 yrs and all had colitis for > 18yrs.

Conclusion: Patients with PSC and longstanding UC have a considerably increased risk of developing colorectal adenocarcinoma post liver transplantation and should be screened aggressively.

390 WORLDWIDE TRENDS IN MORTALITY RATES FOR HEPATOBIILIARY AND PANCREATIC TUMOURS, 1979–1997

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Background: The age-standardised mortality rate (ASMR) per 100,000 population for hepatocellular carcinoma (International Classification of Disease-9 155.0) is increasing in several countries including USA and Japan; but in England & Wales we previously reported an increase in ASMR for intrahepatic cholangiocarcinoma (ICD-9 155.1) only. To investigate this further we analysed mortality statistics from North America, Japan, Australia and Europe to compare ASMR of subcategories of hepatobiliary and pancreatic tumours.

Methods: ASMR for men and women for subcategories of liver tumours (ICD-9 155), tumours of the gall bladder and extrahepatic biliary tree (ICD-9 156) and pancreas (ICD-9 157) from 1979 to 1997 were obtained from the World Health Organisation mortality database.

Results: We confirmed increases in ASMR for hepatocellular carcinoma in those countries were previously reported, but also found significant rises in other countries, particularly France (2.4 to 7.6). There was also an increase in ASMR for intrahepatic cholangiocarcinoma in nearly all countries studied, with large rises seen in Scotland (0.2 to 1.0), Australia (0.1 to 0.7) and USA (0.2 to 0.6). There was a general downward trend in extrahepatic and pancreatic malignancies, with the exception of Southern European countries and Japan.

Conclusion: We confirm previous studies of rising death rates from hepatocellular in several countries, although the trends were not uniform amongst all countries. We also present a hitherto unreported rise in mortality rates for intrahepatic cholangiocarcinoma across 4 continents. This cannot readily be explained by diagnostic transfer from other tumour types, or by improved diagnosis and reporting. Future research on cholangiocarcinoma should include epidemiological studies to examine possible case-clustering and investigation of potential aetiological agents including environmental toxins. ASMR from hepatobiliary and pancreatic tumours are not static and require close future monitoring.

391 POSITIVE CRITERIA FOR PREDICTING MALIGNANCY IN BILIARY BRUSHING CYTOLOGY

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A total of 125 patients with biliary stricture and tumour masses had brushing cytology over a period of 3 years (1997–2000). One hundred and thirty five biliary brushing specimens with a known outcome were reviewed. On review an additional category of atypical probably benign was added (table). The review was carried out blind with no clinical or outcome information by two pathologists. On review the following criteria was considered indicative of malignancy: increased nuclear size, convoluted nuclear outline, abnormal chromatin pattern, increased nucleolar area and numbers, loss of cohesiveness and overlapping of nuclei. Only the negative for malignancy and malignant categories of test result were used to determine the value of the test. The results were as follows:

Abstract 391, Table 1

Result	Inadequate	Negative	Atypical	Suspicious	Malignant
Original	7 (6%)	56 (47%)		19 (16%)	37(31%)
Review	10 (8%)	14 (12%)	21 (18%)	13 (11%)	61(51%)

Both originally and on review the specificity and the predictive value of a positive result were 100%. However on review the accuracy increased from 60% to 89%, the sensitivity increased from 50% to 88% and the predictive value of a negative result increased from 34% to 43%.

Conclusion: The use of additional criteria have resulted in a marked improvement in the accuracy of malignant diagnosis in biliary brushing cytology.

392 HAEMODYNAMIC EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF LOW DOSE CARVEDILOL, A VASODILATING BETA-BLOCKER IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION

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Carvedilol is a non-selective vasodilating beta-blocker with weak alpha-1 receptor antagonism. It has 2-4 times greater beta-blocking action than propranolol. It is thought to reduce intrahepatic resistance.

Aims: To assess the haemodynamic effects and patients tolerability of the acute and chronic administration of low dose carvedilol.

Study design: 10 patients with mean age 54±12 years were studied. Causes of cirrhosis were alcohol-7, primary biliary cirrhosis-1, and hepatitis C-1. Childs grade: A-1, B-6, C-3. 2 patients had ascites and 4 ascites in the past. Following baseline haemodynamic measurements patients were administered 12.5mg of oral carvedilol and the measurements repeated 1 hour later. The patients continued taking 12.5mg carvedilol daily for four weeks and the study was then repeated.

Results: Following acute administration of carvedilol, there was a 23% reduction in the hepatic venous pressure gradient (HVPG) from 16.37±2.14 to 12.56±3.91 mmHg ($p<0.05$), mainly due to a reduction in the wedged hepatic venous pressure (WHVP), with significant falls in the mean arterial pressure, pulse and cardiac output. Chronic administration resulted in a further fall in the HVPG from a baseline of 16.37±0.71 to 9.27±1.40 mmHg ($p<0.001$). The hepatic blood flow fell significantly from 1724.92±435.02 to 718.16±179.28 ml/min ($p<0.05$, $n=5$) following acute dosing, and this reduction was maintained chronically with no effect following rechallenge. The mean arterial pressure, cardiac output and systemic vascular resistance were unaffected after chronic administration and following rechallenge with carvedilol. Liver function tests and serum creatinine were unaffected. One Child's C patient became hypotensive and completed the acute phase of the study. There were no other patient dropouts or adverse side effects noted.

Conclusions: In this study carvedilol at a dose of 12.5mg was well tolerated and resulted in a significant fall of over 40% in the HVPG. This makes it one of the most potent portal hypotensive pharmacological agents, and is worthy of further investigation in large randomised trials to assess its effect in preventing variceal haemorrhage.

393 THROMBIN IN GASTRIC VARICES

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Background: The management of gastric variceal haemorrhage remains a clinical challenge. We carried out a retrospective study to investigate our experience in the use of thrombin for treating gastric variceal bleeding.

Patients and methods: We reviewed the case records of twelve patients who presented to our hospital over a two year period, with gastric variceal bleeding requiring human thrombin treatment. 11 were males and the mean age was 52 years (range 26-83 years). The underlying diagnoses were cirrhosis in 9, portal vein thrombosis in 2 and liver metastasis in 1 patient. 4 of the cirrhotics were Child's A, 3 Child's B and 2 Child's C. 10 patients had fundal gastric varices, 1 had gastro-oesophageal junction varices and the last was not

stipulated. At endoscopy, 6 were found to have actively bleeding gastric varices, 4 had stigmata of recent haemorrhage and in 2, the diagnosis was presumptive. 9 had concomitant oesophageal varices, none of which were thought to have bled. 8 received thrombin as primary treatment whilst 4 had thrombin only after failing TIPSS. Patients received 1-4 sessions (mean 1.9) of thrombin with a mean total dose of 1833units (range 800-4000). Mean follow up was 17.8 months for those still alive (range 7-33).

Results: Hemostasis in the acute setting was achieved in all 12 patients. In the longer term, 9 (75%) had no further bleeds. Of these, 5 patients (42%) did well with thrombin alone, 1 died of metastatic cancer and the other 3 went on electively to TIPSS, splenectomy and a distal splenorenal shunt respectively. 3 patients rebled from their gastric varices 10, 47 and 168 days after first receiving thrombin. 1 was successfully retreated with thrombin but the other 2 died. Only 1 death was related to variceal bleeding. No adverse reactions or clotting derangements were noted. 1 patient however, had gastric variceal bleeding witnessed endoscopically after thrombin injection. This necessitated transfusion but resolved spontaneously.

Conclusions: Our experience demonstrates that endoscopic therapy with thrombin injections alone is safe and can be highly effective in the management of gastric variceal bleeding.

394 PROSPECTIVE STUDY OF LIVER DYSFUNCTION IN PREGNANCY IN SOUTH WALES

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Background and aims: Liver disease is uncommon in pregnancy but has serious consequences. Its frequency varies according to country and ethnic origin and is not documented in Wales. We have prospectively determined incidence, causes and outcome of liver dysfunction in pregnancy in an obstetric unit in South Wales.

Methods: A central laboratory identified all abnormal liver tests from patients in antenatal clinics and wards of an obstetric unit serving a population of 270,000. During the sixteen-month study, there were 4637 deliveries. Patients with abnormal tests (bilirubin > 25µmol/L, aspartate transaminase (AST) > 40U/L and/or gamma GT (γGT) > 35U/L) were studied prospectively on receipt of blood results and medical advice was provided to obstetricians. Clinical course of mother and fetus/infant was recorded.

Results: 140 patients had abnormal liver tests: elevation of AST in 115 (range 41 - 9299), γGT in 58 (range 36 - 278) and bilirubin in 24 (range 26-155). Thrombocytopenia ($< 150 \times 10^9/L$) was seen in 33, raised bile acids in 18 (range 23 - 149 µmol/L) and hyperuricaemia in 32 (range 0.41 - 0.70 µmol/L). Hepatobiliary ultrasound scan (USS) was abnormal in 8. There were 173 diagnoses amongst 131 patients: pre-eclampsia 63, obstetric cholestasis (OC) 21, HELLP syndrome 15, hyperemesis gravidarum 10, acute fatty liver 5, sepsis 12, post-Caesarean section 22, bile duct stones 3, placental pathology 9, diabetes 6, drug toxicity 5, hepatic haematoma 1 and chronic hepatitis C 1. Elevation of AST was the predominant abnormality in OC. There were no maternal deaths but there was one intrauterine death at 30 weeks associated with pre-eclampsia. Sixty five patients required delivery by induction or Caesarean section to improve hepatic function. Thirty seven babies required admission to special care unit.

Conclusions: Liver dysfunction was seen in 140 of 4637 pregnancies (frequency 1 in 33) during a sixteen-month prospective study. Transient but sometimes serious effects on maternal and infant morbidity were observed but there were no maternal deaths and only one stillbirth.

395 HOW WELL TOLERATED IS DAY CASE LIVER BIOPSY?

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It is recognised that day case liver biopsy is under-utilised in UK hospitals. Little is known about post discharge events in patients having this procedure.

Patients/methods: All patients satisfying BSG criteria for day case liver biopsy have been followed up to establish post discharge morbidity. Patients follow a structured protocol, identifying route for readmission if necessary. All patients are contacted by nursing staff 24 hours post procedure to establish the need for analgesia, GP visit and hospital admission. A total of 147 patients have been studied over 39 months (61 female 86 male) median age 40 years. Indication for

biopsy was Hepatitis C 94, Investigation of Abnormal Liver function 26, Autoimmune Hepatitis 5, Post Bone Marrow Transplant 5, Primary Biliary Cirrhosis 4, Methotrexate therapy 4, Haemochromatosis, Iron overload 7, Hepatitis B 2.

Biopsy method, Trucut needle n = 100, Trucore biopsy gun n = 47. Number of passes, 1 pass n = 119 (80.95%), two passes n = 25 (17%), three passes n = 3 (2.04%)

Results: 145 patients were discharged on the same day, 2 (1.36%) required overnight stay for observation. 139 of 145 were contacted by telephone the next day. 43 (29.25%) required analgesia at home. 4 (2.72%) called out GP. 3 (2.04%) returned to the hospital for review, one patient required readmission. (0.68%). 21% of patients biopsied with a trucore biopsy gun required analgesia at home while 33 % biopsied by trucut needle required analgesia at home.

Conclusion: (1) Day case liver biopsy is safe in selected patients. A significant number of patients suffer post discharge pain requiring analgesia but little other morbidity was observed. (2) The use of the Trucore biopsy gun may reduce the need for analgesia post biopsy.

396 POPULATION-BASED EPIDEMIOLOGY OF LIVER ENZYME TESTS: EVALUATING NORMAL AND ABNORMAL TESTS IN TAYSIDE, 1991-97

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Liver function tests are routinely performed in primary and secondary care. Studies have quantified the incidence of liver enzyme abnormalities, but neglect subjects that subsequently retest normal or do not retest at all. The aim of this study was to evaluate the epidemiology of liver enzyme abnormalities and the consequences for all subjects with initial abnormal liver function tests (ALF tests).

Methods: All liver enzyme and albumin and bilirubin tests from 1991 to 1997 were identified from a biochemistry data set and record-linked with the ELDIT database of liver disease. Tests include ALP, ALT, GGT, albumin and bilirubin with dates and results. Descriptive epidemiology and comparison with outcome were done electronically.

Results: There were 1,065,570 liver enzyme and 588,416 albumin and bilirubin tests performed in the study period. The median age of ALF tests ranged from 58-67 years with 12-17% of the people tested having an ALF test results. The mean incidence per year of ALF tests ranged from 489 to 869 per 100,000 people. In a series of tests, a large number of people had an ALF test last and never returned for testing (range from 8187-15742). Death and migration may account for some, but not all. Approximately 6000 people had an ALF test on their first test and never return for subsequent testing. Only 10% of the abnormal GGT+ALP+ALT are accounted for in existing liver disease, most of which is alcoholic liver disease (155/499).

Conclusion: Preliminary results indicate a sub-population of abnormal liver function tests that are not accounted for in an existing liver disease database. Temporal analysis may show these subjects as having precursor ALF tests for future liver disease.

397 THE EFFECT ON TOXICITY ON REDUCING THE SIZE OF AVAILABLE PARACETAMOL PACK SIZES

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Introduction: Paracetamol overdose is a common cause of hepatotoxicity and death, and the incidence has been increasing. As a means of reducing harm, the Medicines Control Agency limited the pack size of over-the-counter paracetamol in September 1998. This change has had variable effects possibly due to differences in case ascertainment. We have used the measurement of serum paracetamol levels to determine paracetamol overdose rates for patients presenting to Ninewells Hospital, Dundee.

Method: The biochemistry database was searched for all paracetamol assay requests for each 12-month period from September 1995 to September 2000. We recorded all requests, all assays with measurable paracetamol and all results with levels that were potentially hepatotoxic 4 hours after ingestion (> 1.3 mmol/l).

Results: A total of 6336 tests were performed of which 4454 (70.1%) were negative for paracetamol.

Abstract 397, Table 1

	95/96	96/97	97/98	98/99*	99/00*
All tests	1063	1380	1365	1168	1346
All +ve tests	319	362	403	358	440
>1.3 mmol/l	23	27	27	27	28

*Pack-size change.

Conclusion: These results do not suggest that the incidence of paracetamol overdose has been affected by the over-the-counter pack size reduction at least in the Tayside region of Scotland. Further measures to reduce the burden of paracetamol overdose to the health-care system must be considered.

398 A NOVEL ¹³C₂ BREATH TEST FOR THE NON-INVASIVE ASSESSMENT OF SYNTHETIC LIVER FUNCTION IN-VIVO

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Objective: We set out to design a ¹³C₂ breath test that could serve as a quantitative liver function test in patients with liver disease but which, in contrast to mainstream research, would not probe for enzyme activity of the cytochrome P450 type.

Design and methods: We used a ¹³C-labelled amino acid as probe to assess performance of phase II conjugation pathways. Breath samples were collected over three hours at timed intervals and subsequently analysed on a gas - isotope ratio mass spectrometer for ¹³C abundance in exhaled CO₂. Raw data were converted into percentage dose recovery (PDR) and cumulative PDR. Time to peak PDR was recorded also.

Results: In a pilot study, control values for apparent glycine conjugation and time to peak PDR were established from 11 healthy volunteers; 5 male, 6 female, aged 28 - 62 yrs. These values were compared with data obtained from 8 patients (4 male, 4 female, aged 33 - 60 yrs) with proven liver disease of different etiology and severity. One patient suffered from auto-immune chronic hepatitis, one from hepatitis C and alcohol induced cirrhosis, all others suffered from alcohol induced cirrhosis. Results of this pilot study are presented in the table.

Abstract 398, Table 1

	Controls (n = 11)	S.D.	Patients (n = 8)	S.D.
Apparent amino acid conjugation [%]	40.83	±6.57	9.74	±13.36
Time to peak PDR [min]	53.5	±5.3	92.5	±16.9

Conclusion: Apparent amino acid oxidation and time to peak PDR provide good discrimination between cirrhotic and non-cirrhotic individuals. The encouraging results of this pilot study warrant further investigation (a) to establish sensitive and specific cut-off values and (b) to assess the prognostic value of this new test.

399 TISSUE TRANSGLUTAMINASE ANTIBODIES AND COELIAC DISEASE IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS AND AUTOIMMUNE CHOLANGITIS

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Background: Recent studies have reported an association between coeliac disease (CD) and primary biliary cirrhosis (PBC). Tissue transglutaminase (tTG) is the main autoantigen recognized by endomysial antibodies (EMA), the best serological marker of CD so far.

Aims: To assess the efficacy of IgA antibodies to tTG in screening a group of Cretan patients with PBC and autoimmune cholangitis (AIC) for CD.

Materials and methods: Sera from 62 patients with PBC, 17 with AIC, and 100 healthy blood donors were examined for IgA-tTG by a guinea-pig ELISA, for IgA EMA and reticulin antibodies (ARA) by

indirect immunofluorescence, and for IgG- and IgA-gliadin antibodies (AGA) by an ordinary ELISA. Ten serum samples from biopsy-proven CD patients were served as methodological controls.

Results: AGA were detected with a significantly increased frequency in patients with both PBC and AIC (21% and 35% vs 3% respectively, $P < 0.001$). IgA-tTG were also found in 6 of 62 PBC patients (10%), in 3 of 17 patients with AIC (18%), in all of 10 CD patients, but not in blood donors. ARA and AMA were negative in patients with PBC and AIC and in healthy controls. Intestinal biopsies were performed in 47% of PBC and in 71% of the AIC patients with at least one antibody positive. No evidence of coeliac disease was found.

Conclusions: Our findings do not support the association between PBC, AIC and CD. In liver disease gliadin and transglutaminase antibodies are not useful in screening for CD, whereas the EMA test and intestinal biopsy remain the gold standard.

400 THE INFLUENCE OF PRE-ADMISSION DIET UPON LIVER FUNCTION TESTS OF PATIENTS WITH ACUTE ALCOHOLIC HEPATITIS

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Diet has been implicated in the development of alcoholic liver disease. Epidemiological studies suggest a diet high in saturated fatty acid (SFA) is associated with a lower mortality from alcoholic cirrhosis, and polyunsaturated fatty acid (PUFA) is an important factor for the development of alcoholic liver damage in rat models. The role of diet in the acute presentation of alcoholic hepatitis is unknown.

Aim: To assess the role of pre-admission diet on liver function tests.

Methods: Nine patients presenting with acute alcoholic hepatitis (AAH) diagnosed on clinical grounds were assessed. A detailed history was obtained of their diet over the two weeks prior to admission.

Results: Patients were aged of 44.4 ± 2.8 years with admission serum bilirubin (SB) of 200.1 ± 32.2 . The energy intake was 2928 ± 423 kcal ($49.5 \pm 6.3\%$ from alcohol). Patients with $<8\%$ of energy from SFA had higher admission AST (342.7 ± 72.1 cf 128.6 ± 11.5 ; $p < 0.02$) and SB (280.8 ± 43.0 cf 137.0 ± 18.1 ; $p < 0.02$). Correlations of admission AST, but not ALT, and SB were as follows:

Abstract 400, Table 1

	% kcal: Fat	% kcal: SFA	% kcal: PUFA	% kcal: Alcohol	% RDI of Fat
AST	r -0.799; p<0.01	r -0.869; p<0.005	r -0.712; p<0.05	r 0.822; p<0.01	r -0.798; p<0.01
SB	r -0.673; p<0.05	r -0.715; p<0.05	p=NS	r 0.736; p<0.05	r -0.674; p<0.05

Estimated dietary intake of vitamin C, selenium or vitamin B6 did not appear to affect standard biochemical liver function tests, nor did diet correlate with the prothrombin time or discriminant function.

Conclusions: AST activity and SB in AAH appear to be related to the amount of fat, particularly SFA, and alcohol in the diet. As AST derives from mitochondria, a low fat diet, especially if low in SFA, with a high % calorie intake as alcohol may predispose to mitochondrial dysfunction. Pre-admission diet may therefore significantly modify the expression of acute alcoholic hepatitis.

401 ALCOHOL CONSUMPTION PATTERNS IN HEAVY DRINKERS WITH AND WITHOUT ALCOHOLIC LIVER DISEASE (ALD)

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Background: The risk of ALD increases with increasing alcohol consumption; it is unclear whether the risk is also related to drinking pattern or to type of alcoholic beverage consumed.

Aim: To compare patterns of lifetime alcohol intake in two previously characterised (Hepatology 2000 32:A420) cohorts of heavy drinkers (>60 U/wk(M) or 40 U/wk(F) for >5 yr): one with decompensated ALD (patients: $n=147$, 107 M, age $48 \pm SD 10$ yr) and one with no clinical, laboratory or ultrasound evidence of serious liver disease (controls: $n=101$, 79M, age 48 ± 9 yr).

Methods: Lifetime total alcohol intake (LTA) and intake of beer/lager, spirits, wine/sherry and cider to first decompensation (patients) or to interview (controls) was assessed using the time-line follow back method. Correlation of LTA between repeated testing and between spouse estimates was 0.86 ($n=9$) and 0.81 ($n=9$) respectively.

Results: LTA was higher in controls (median 138840U, IQR 100776–190424) than in patients (median 114712, IQR 80262–165984); $p < 0.02$ by Mann-Whitney (M-W). Spirit, wine and cider consumption increased with time in both cohorts; in contrast, beer/lager consumption either did not change (patients) or fell (controls). Controls drank more beer/lager (median 103064, IQR 41912 to 156312) than did patients (median 61,152, IQR 21658–109733); M-W $p < 0.01$. In contrast, spirit consumption tended to be higher in patients (median 0U, IQR 0–54080) than in controls (median 0U, IQR 0–25688); whilst this difference was not significant by M-W, the distribution of patients tended towards higher levels of spirit consumption than did that of the controls (2×5 Chi2 16.9; $p < 0.05$). Cider and wine consumption did not differ between the cohorts. The proportions of time spent in constant drinking (≥ 5 days/wk), weekend-only drinking, binge drinking and abstinence were similar in the two cohorts.

Conclusion: These data point towards the existence of factors other than total alcohol consumption in the development of ALD.

402 EVIDENCE A REDUCTION IN HEPATIC PERFUSION DURING EARLY ABSTINENCE IN ACUTE ALCOHOLIC HEPATITIS

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Background: It has been noted that patients with acute alcoholic hepatitis (AAH) often worsen several days after admission to hospital and abrupt cessation of alcohol. The reason for this deterioration is unknown.

Aim: We aimed to assess hepatic perfusion and uptake of colloid by Kupffer cells in 10 patients with AAH within 3 days of alcohol cessation.

Methods: Each patient underwent paired liver sulphur colloid scans: early (day 1–3) and late (day 7–9) after admission. First-pass hepatic arterial (G1) and portal venous gradients (G2) were measured and the hepatic perfusion index (HPI%) was calculated using the formula $G1/G1+G2 \times 100\%$. Overall uptake in the liver was assessed relative to that of the vertebral bodies (L/V ratio).

Results: The patients had a mean Discriminant Function (DF) of 45.4 ± 6.8 . All patients survived the episode of AAH. Changes seen between early and late scans are shown:

Abstract 402, Table 1

	G1	G2	HPI%	L/V ratio
Early	44.5 ± 28.0	-0.8 ± 12.8	98.9 ± 27.8	1.4 ± 0.88
Late	34.6 ± 17.5	$7.0 \pm 8.0^*$	$82.9 \pm 18.3^*$	1.6 ± 0.89

* $p < 0.05$ * $p < 0.05$

The HPI% correlated with the ALT ($r = -0.804$; $p < 0.01$) and AST ($r = -0.707$; $p < 0.05$). The portal gradient correlated with the prothrombin time ($r = -0.803$; $p < 0.01$) and DF ($r = 0.726$; $p < 0.02$). The L/V ratio did not change throughout the study period but correlated with serum albumin ($r = 0.689$; $p < 0.05$).

Conclusions: Kupffer cell function is impaired at the time of admission with AAH and this dysfunction persists throughout the first 7–10 days. Hepatic perfusion however diminishes during this period of time and may explain why patients who are ill on admission often become more so during the second week of hospitalisation.

403 STUDY OF ACUTE LIVER FAILURE IN SCOTLAND

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Introduction: Acute liver failure (ALF) is a devastating condition which although rare retains a high mortality. New information on its incidence and outcome are important in planning for this condition.

Aims: (1) To accurately describe the incidence and outcome of ALF in Scotland. (2) To determine the contribution that social deprivation has in determining outcome in patients with ALF.

Methods and patients: Data was prospectively collected for 227 ALF admissions to the Scottish Liver Transplant Unit (SLTU) from 1992–2000. Trey and Davidson's definition of ALF was used. Information was collected on outcome, consideration for transplant and markers of social deprivation (DEPCAT score).

Results: The incidence of all cause ALF and paracetamol-induced ALF (POD) in Scotland in 1999 was 0.588/100,000 and 0.4/100,000 population respectively and has not changed. The mean age of patients was 36.9 $\pm$ 0.93 years; 39.2% were male and 60.8% female. The causes of ALF were paracetamol (74.0%), Non-A-E hepatitis (6.17%), idiopathic (5.73%) & idiosyncratic drug reactions (4.85%). Of the 168 POD patients, 80 met the King's College Poor Prognosis Criteria (KCPP criteria) and 39 were listed for OLT. Of these 25 were transplanted and 14 died before OLT. Of the 41 patients not considered suitable transplant candidates 1 spontaneously recovered. Of the 88 patients who did not meet the King's College poor prognosis criteria 18 died. The commonest reasons for not listing POD patients were ongoing alcohol dependence (29.3%), patients were too sick for transplant (24.4%) or significant psychiatric illness (22%). The commonest cause of death in POD patients was multi-organ failure (70.8%) and refractory elevations of ICP (23.6%). The POD group contains a greater proportion of patients with higher social deprivation scores compared with all causes of ALF ($p=0.04$). There is no relationship between DEPCAT score and other outcomes such as meeting of KCPP criteria, listing for OLT or death.

Conclusion: (1) Paracetamol remains the commonest cause of ALF in Scotland and has not decreased after legislative changes. (2) Only 51.2% of POD patients meeting KCPP criteria were listed for OLT. (3) Whilst social deprivation in Scotland is associated with a higher rate of paracetamol-induced ALF, there was no difference (by DEPCAT score) in outcomes such as ALF severity, consideration for transplant or death.

404 HEALTH RESOURCE USE AND COSTS ASSOCIATED WITH VIRAL HEPATITIS

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The true size of the problem of chronic viral hepatitis is becoming apparent, the real costs in population terms have only so far been modelled. This study examined the health resource use and costs associated with chronic viral hepatitis from diagnosis, compared with the general population. Cause of death was also examined.

Methods: A purpose-built register of liver disease in Tayside, ELDIT, was used. The study population comprised residents of Tayside, Scotland in the study period 1991 to 1997. Subjects HCV or HBsAg positive were identified from ELDIT. Two comparators from the general population were allocated by age (5 year band)-sex frequency matching. Hospital admissions and prescription data were record-linked to identify health resources used. Cause of death was ascertained from death registries.

Results: HBsAg positive subjects were more likely to be hospitalised, (OR 1.1; 95% CI 0.8–1.7) and length of stay was longer but neither was significantly more than the comparators. The average cost of hospitalisation per HBsAg positive subject was £2939 greater than the comparator group. HBsAg subjects were more likely to be readmitted to hospital (3.9 vs 1.7 readmissions) and die of diseases associated with the liver. Hepatitis C subjects were more likely to be hospitalised (OR 2.7; 95% CI 2.1–3.6), stay in hospital longer (5.5 vs 4.6 days; p -value=0.001) and have more readmissions to hospital (5.0 vs 1.6) than their comparators. The average cost of hospitalisation per hepatitis C subject was £4172 greater than the comparator group. Hepatitis C subjects were more likely to use prescription medication (e.g. Anxiolytics OR 8.8; 95% CI 6.7–12.0) and die of complication of the immune system or substance abuse.

Conclusion: This study starts to demonstrate the increased costs of chronic viral hepatitis. It illustrates that the costs of the hepatitis C epidemic are not to be incurred at some distant date in the future but are already having to be paid for.

405 DISTINCT FUNCTIONAL PATTERNS OF HBV-SPECIFIC CD8+ CELL RESPONSE IN HEPATITIS B VIRUS INFECTION

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Introduction: The range of manifestations of HBV infection suggests a degree of variability in host/virus interaction. We analysed longitudinally the frequency and function of HBV-specific CD8 cells in different disease profiles of hepatitis B.

Methods: 15 HLA-A2+ subjects were studied longitudinally for 9–24 months, with 3 subjects in each group: resolved acute hepatitis B: Gp A (HBV DNA undetectable, ALT normal); chronic hepatitis B: Gp B (HBV DNA <1pg/ml, ALT <40IU/L); Gp C (HBV1–10, ALT 40–80); Gp D (HBV >100, ALT >80); Gp E (HBV >100, ALT <40). Core, envelope, and polymerase-specific CD8 cells were directly analysed by flow cytometry, after staining with HLA-A2/HBV peptide tetramer complexes. In parallel, expansion capacity and γ IFN production of CD8 cells specific for 11 HLA-A2 restricted epitopes was tested. Frequency of intrahepatic HBV-specific CD8 cells was obtained at liver biopsy in all patients in groups C-E.

Results: Differences in direct cell frequency were seen in liver, where HBV-specific CD8 cells were virtually undetectable in groups D and E (0.02–0.3% of CD8), but clearly detectable in group C (0.9–1.4% of CD8), whereas the circulating frequency of these cells was usually not above background frequency. In contrast, different patterns of circulating HBV-specific CD8 were demonstrable when expansion capacity and γ IFN production of expanded CD8 cells was tested. Gp A showed greatest potential for multispecificity (at least 3 of 11 HBV specificities). Although HBV-specific CD8 cells in chronic patients showed a reduced ability to expand in vitro, a multispecific CD8 response was repeatedly present in Gp C patients, whereas this pattern was present only during a flare of disease (ALT 1200 U/L) in one patient in Gp D, and was entirely absent in Gp E. Of interest, patients in Gp B, who control HBV without clinical liver injury, demonstrated only a mono/oligoclonal response.

Conclusion: This study shows that patients chronically infected with HBV possess a heterogeneous pattern of virus-specific CD8 response, suggesting that the understanding that chronic hepatitis B may be characterised by a failure to expand a multispecific CD8 cell response merits reappraisal.

406 PRECORE HBV MUTANT INFECTION IS MORE COMMON THAN EXPECTED AMONG HBV CARRIERS IN SCOTLAND

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Background: Chronic Hepatitis B is uncommon and HBV precore mutant infection is presumed to be low in Scotland.

Aims: 1) Compare HBeAg(+) with AntiHBe(+) carriers 2) Analyse virological characteristics of AntiHBe(+) carriers

Method: Review of 109 chronic HBsAg(+) patients referred to our centre from Jan.'89 to Dec.'98. PCR (qualitative and semi-quantitative) for HBV DNA in Anti e (+) patients and molecular sequencing of DNA(+) samples for the HBV precore mutant.

Results: 1) 65(60%) patients were Anti e (+) and 44(40%) e Ag(+). No difference was found in epidemiological and clinical features except sexual transmission being more common in the e Ag(+) group ($p<0.001$). 35/65(4%) of Anti-e (+) patients had raised ALT, the mean of which was 4x ULN and this did not differ significantly from that in the e Ag(+) group. Liver histology results were also similar between e(+) and Anti e (+) patients with >90% showing features of chronic hepatitis +/- cirrhosis. 2) 27/35 (80%) Anti e (+) patients with raised ALT levels had liver biopsies and all were abnormal; 26/27(96%) showed features of chronic hepatitis +/- cirrhosis. 47/65 serum samples were analysed and 39/47(83%) found positive for HBV DNA (>50 copies/ml serum). 29/39(74%) had the A1896 precore HBV mutant. 10/29 (34%) were British patients. 21/29(72%) had HBV DNA levels >5000 copies/ml. Quantified DNA were also found to correlate positively and significantly with ALT. (Pearson 2-tailed correlation: $r=+0.7$, $p=0.0$).

Conclusions: 1) HBV carriers, whether e Ag(+) or Anti e(+), were comparable in epidemiological, clinical, biochemical and histological characteristics. 2) 54% Anti e(+) patients presented with raised ALT; of these virtually all had chronic hepatitis +/- cirrhosis. 3) Ongoing viraemia was detected in >80% of Anti e(+) patients. 4) 74% of Anti e(+)/DNA+ patients had the classical precore HBV mutant. 5). Quantified HBVDNA levels correlated positively and significantly with ALT levels.

407 NEURAL NETWORKING IN HEPATITIS C PATIENTS TO PREDICT KNODELL SCORES

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Hepatitis C is a relatively common disease and prone to chronicity. Liver biopsy and grading by the Knodell method in a patient with chronic Hepatitis C provides valuable information regarding treatment but is associated with a certain degree of risk. Recently published work [Tharakan] proposes clinical algorithms to predict the Knodell score in Hepatitis C patients. It is anticipated that accurate predictions of the score could make liver biopsies obsolete.

We aimed to test this hypothesis by building and training suitable neural networks and prospectively validating our predictions in a single blinded manner. Our system builds and validates training, evaluates them, selects the top networks, throws in a few mutations and goes back into the training/testing cycle back again. Data from 20 Hepatitis C patients were used as input variables. Neural networks were built and trained from these data with the best networks chosen to predict the Knodell score. The data from 25 Hepatitis C patients including genotype, AST level, age and past medical history of blood transfusions, operations, and tattooing were forwarded to us from two different centres, which formed a set of variables. Prediction of the Knodell score was elaborated for each individual patient using the best neural networks elaborated previously from the initial core of twenty patients. Our predictions of the Knodell score were then compared with the actual values obtained from two independent Histopathologists. We used student t-tests to compare the group of predicted versus actual values of the Knodell score.

Predicted versus actual values of the Knodell score correlated highly significantly ($p < 0.0001$). Predictions of the Knodell score were possible at an over 95% accuracy level.

It is concluded that neural networks may be useful to predict the Knodell score with a high level of accuracy. Liver biopsies for the assessment of Hepatitis C patients in order to make treatment decisions may therefore be avoided.

408 ACUTE AND CHRONIC EFFECTS OF INTERFERON ALPHA THERAPY ON MOOD AND THE HYPOTHALAMIC PITUITARY ADRENAL (HPA) AXIS IN PATIENTS WITH CHRONIC HEPATITIS C

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Background: Fatigue and depression are common sequelae of interferon alpha therapy. The pathogenesis of this is unclear. Interferon at low doses (≈ 5 million units) is known to stimulate the HPA axis. Dysregulation of this axis occurs in up to 60% of patients with major depression.

Aims: (1) To determine if low dose Interferon α / Ribavirin combination effects the HPA axis and (2) To determine if major depression secondary to Interferon α was associated with chronic hypercortisolaemia.

Methods: 10 patients with chronic hepatitis C were assessed before treatment {with Interferon α and Ribavirin}, 30mins following 3 million units of interferon α , and after 1 month of combination treatment. Serum cortisol was evaluated by estimation of the mean cortisol value of 10 sequential samples taken between 1pm to 4pm, at twenty minute intervals, on the test days as outlined above {Halbreich method}.

Cortisol response to dexamethasone suppression {Carroll et al}, was assessed at baseline and after one month. Mood was assessed by structured interview {Hamilton depression rating scale; HM-D}, DSM-IV checklist and self report {Beck Depression Inventory; BDI}.

Results: There was a significant increase in fatigue and depression scores measured by both BDI, {10.7 +/- 4.8 before compared to 15.3 +/- 5.0} after one month of treatment., and by HAM, { 3.8 +/- 1.8

before compared to 11.8 +/- 2.8 } after one month of treatment with combination therapy {Interferon α /Ribavirin}. 30% of patients fulfilled criteria for DSM-IV major depression after one month of treatment. None of the patients demonstrated dexamethasone suppression at baseline or on follow up and there was no significant change in mean cortisol { 271.7 +/- 39.9 vs 260.6 +/- 28.5 nmol/l, $p=0.81$ }. Serum cortisol did not change during the first 3.5 hours following low dose Interferon α .

Conclusion: In contrast to high dose Interferon α , low dose Interferon α does not stimulate the HPA axis either acutely or chronically. Depression, which we observed in 30% of subjects taking Interferon α /Ribavirin, may occur via other mechanisms eg. Proinflammatory cytokine activation and we are currently investigating this possibility.

409 VALIDATION OF THE REVISED INTERNATIONAL AUTOIMMUNE HEPATITIS GROUP (IAHG) SCORING SYSTEM: EXPERIENCE IN THE NORTH OF ENGLAND

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Introduction: Autoimmune hepatitis (AIH) is a chronic necro-inflammatory liver disease of unknown aetiology. Diagnosis demands exclusion of other causes of liver disease. The IAHG has recently established a revised scoring system to define definite & probable AIH (*J Hepatol* 1999; 31: 929-38). We aimed to apply this revised scoring system to a series of patients diagnosed as AIH from the North of England, in order to verify its sensitivity and specificity.

Patients and methods: 106 patients diagnosed as AIH between June 1972 - March 2000 from 11 hospitals in our region were enrolled in this retrospective study (87 F, 19 M; mean age at presentation 49.27 yrs $\pm$ 16.57, mean follow-up 6.64 yrs $\pm$ 5.3). The medical records of all patients were reviewed, data required for the IAHG score were entered onto an anonymous database, and the score was calculated for each patient (pre-treatment: definite AIH >15, probable AIH 10-15, post-treatment: definite AIH >17, probable AIH 12-17).

Results: At presentation 43 (41%) patients had cirrhosis. 91 (85%) patients had "classic" Type 1 AIH with +ve antinuclear antibody (ANA) and/or smooth muscle antibody (SMA). 8 patients presented <20 yrs of age, 9 at 21-30 yrs, 14 at 31-40 yrs, 19 at 41-50 yrs, 40 at 51-65 yrs and 16 at >65 yrs of age. Pre-treatment mean IAHG score was 18.4 $\pm$ 3.7, 81 with definite, 22 with probable, 3 with score <10 [One with +ve ANA but history of exposure to Diclofenac, one with +ve SMA but histology compatible with autoimmune cholangiopathy, one with +ve ANA but histology compatible with PBC]. Post-treatment mean IAHG score was 21.4 $\pm$ 3.5, 85 with definite, 18 with probable, 3 with score <12. During follow-up 10 pts have received a liver transplant, & 4 patients have died, one with hepatocellular cancer.

Conclusions: This study demonstrates that the revised IAHG criteria will be generally applicable in clinical practice in defining disease groups. Patients with the "classic" condition can be distinguished from those with variant forms of AIH.

410 INTEGRIN RECEPTOR EXPRESSION CHANGES IN DISEASED HEPATIC STELLATE CELLS

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The extracellular matrix (ECM) is now recognised as exerting a powerful influence on cell phenotype. Hepatic stellate cells are the principal effectors of liver fibrosis. If isolated and maintained *in vitro* on a normal basement membrane-like matrix such as matrigel, they remain quiescent, poorly proliferative cells, producing small amounts of normal basement membrane proteins, such as type IV collagen and fibronectin. If, however, the cells are cultured on type I collagen, representing the 'scar' matrix of cirrhosis, they rapidly transform into a highly proliferative myofibroblast-like phenotype, producing greatly increased quantities of type I collagen. The communication between cells and their ECM is through cell surface receptors called integrins. These are heterodimeric transmembrane proteins composed of an α and a β subunit, whose ligands are matrix molecules rather than cytokines. In this study stellate cells have been isolated from normal rat liver and been allowed to transform in culture. In addition, cells have been isolated from normal and diseased human livers. Integrin subunit expression has been detected immunohistochemically.

Abstract 410, Table 1

Cell type	β_1	α_1	α_2	α_3	α_4	α_5	α_6	α_V
Quiescent rat cells	±	+++	±	±	-	±	±	+
Transformed rat cells	+++	+++	++	+	±	+++	++	++
normal human quiescent	+	+	-	-	-	+	-	±
normal human transformed	+++	+++	++	±	±	++	+	+
primary biliary cirrhosis	+++	+++	+	±	±	++	+	+
alcoholic cirrhosis	+++	++	+	±	+	++	+	+
autoimmune cirrhosis	+++	+++	+	±	+	++	±	+
alcoholic hepatitis	+++	+++	+	±	±	++	+	+

The results are summarised in the table above. In rat stellate cells, β_1 , α_2 , α_3 , α_5 , and α_V are all weakly expressed by quiescent cells, and their expression is increased in activated cells. In contrast, α_1 is strongly expressed in both quiescent and activated rat stellate cells. The repertoire of integrins expressed by human stellate cells resembles that of rat stellate cells. As human stellate cells transform, they upregulate the expression of α_1 , α_3 and α_V , with de novo expression of α_2 , α_3 , α_4 and α_6 . The integrin expression in stellate cells isolated from diseased human livers resembles activated rather than quiescent cells. In conclusion, chronic liver injury is associated not only with modifications to the components of the ECM, but also with changes in the expression of ECM receptors. Thus, manipulation of integrin expression or function may lead to new antifibrotic therapies.

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411 THE PREVENTION AND TREATMENT OF MURINE COLITIS USING GENE THERAPY WITH ADENOVIRAL VECTORS ENCODING INTERLEUKIN-10

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Background: Interleukin-10 knockout (IL-10 $-/-$) mice spontaneously develop Th1 T cell mediated colitis with many similarities to Crohn's disease. Daily injections of IL-10 are able to prevent disease onset but do not induce remission in established disease.

Aims: To investigate the therapeutic efficacy and mechanism of action of gene therapy using adenoviral vectors encoding IL-10 (AdvmuIL-10) in the IL-10 $-/-$ mouse model of colitis.

Results: A single systemic injection of AdvmuIL-10 was able to prevent the onset of colitis for at least 10 weeks, but was also sufficient to induce remission in IL-10 $-/-$ mice with established disease ($p < 0.001$ by ANOVA compared to saline or empty vector (Adv0) treated controls). Histological scores were significantly lower in AdvmuIL-10 treated mice than controls ($p < 0.05$). In addition, AdvmuIL-10 therapy reduced the elevated serum amyloid protein levels and stool IL-1 β concentrations characteristic of this disease ($p < 0.05$). IL-10 protein was present in colonic homogenates of AdvmuIL-10 treated IL-10 $-/-$ mice, and the effects of secreted IL-10 were detectable by a sensitive bioassay for at least 10 weeks after injection. The immunoregulatory effect of a single AdvmuIL-10 injection was manifest both by a reduction in TNF- α , IFN- γ and RANTES release from stimulated spleen cell cultures ($p < 0.005$ compared to saline treated controls) and also by a change in the proportion of CD45RB^{high/low} lymphocytes in the spleen compared to control mice ($p < 0.05$ compared to saline treated controls). The delivery of IL-10 appeared to diminish the host anti adenoviral response as serum from IL-10 $-/-$ mice treated with AdvmuIL-10 contained significantly lower titres of neutralising anti-adenoviral antibodies than mice that had received either empty vector or a virus encoding an irrelevant protein - Adv β gal ($p < 0.05$).

Conclusion: Gene therapy strategies using adenoviral vectors encoding immunoregulatory cytokines may prove to be a potent approach for the treatment of chronic inflammatory diseases such as Crohn's disease.

412 ACID 1 STUDY: RESULTS OF A RANDOMISED TRIAL OF *H. PYLORI* ERADICATION IN PATIENTS ON MAINTENANCE ACID SUPPRESSION IN THE COMMUNITY

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Objective: The assessment of community intervention in dyspepsia (ACID1) study investigates the effect of *H. pylori* (*Hp*) eradication in a large community based dyspeptic population irrespective of underlying diagnosis.

Patients/methods: 11,149 of 176,268 patients receiving H₂RA or PPI from 40 general practices were identified. After exclusions those receiving maintenance therapy (≥ 3 scripts/year) were randomised to active (n=4003) or control (n=1707) groups. Active patients were divided according to diagnostic groups: investigated ulcer n=1143 (28.5%); investigated non-ulcer n=1772 (44.3%); and uninvestigated n=1088 (27.2%). Active patients were invited to a nurse led community dyspepsia clinic and received health information, ¹³C Urea Breath Test (UBT) and, where positive, were prescribed *Hp* eradication. Glasgow Dyspepsia Severity Score (GDSS) and Digestive Disease Quality of Life (DDQol) data (0, 6 months) and prescription data (0, 6, 12 months) were collected. Patients receiving *Hp* eradication had repeat ¹³C UBT at 6 months.

Results: 1213 of 2353 (51.6%) patients attending clinic were *Hp* positive. Per protocol eradication rate achieved was 766/937 (80.4%) patients. Mean changes in score for GDSS and DDQ are presented.

Abstract 412, Table 1

<i>Hp</i> Status	N	GDSS	DDQol	Off therapy for 1 year
Successful eradication	766	2.03*	0.27*	39.9%*
Failed eradication	171	1.26	0.14	23%
<i>Hp</i> Negative	898	1.77*	0.11	17.7%

* $p < 0.05$, ANOVA; * $P < 0.05$, X² test versus both other groups.

Conclusions: *Hp* eradication irrespective of underlying diagnosis in a large dyspeptic population on maintenance acid suppression in general practice leads to a significant improvement in symptom and quality of life scores and a significant reduction in prescribing.

413 TGF- α INDUCES A β -CATENIN/TCF MEDIATED TRANSCRIPTION EVENT IN BARRETT'S OESOPHAGUS

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In Barrett's Oesophagus one of the earliest identified events is the up-regulation of the EGF-receptor, and its associated ligand TGF- α . Previous reports have identified a number of alterations in the expression and localisation of cell-cell adhesion molecules, such as E-cadherin and β -catenin of the adherens junction, in the transition from a normal stratified squamous to the metaplastic mucosa of Barrett's Oesophagus. Relocalisation of β -catenin from the membrane to the nucleus induces oncogene expression (a process termed β -catenin / TCF mediated transcription).

In this study we assessed whether the elevated levels of TGF- α could direct the metaplastic-remodeling event observed in the initiation of Barrett's Oesophagus.

Stimulation of both primary and established oesophageal cell cultures with TGF- α for 3 hr resulted in the transition of β -catenin from a membranous to nuclear localisation, as assessed by immunofluorescence. We further identified this transition was associated with tyrosine phosphorylation of β -catenin. Using the TOP-FASH luciferase reporter construct, a measure of β -catenin / TCF mediated transcription, TGF- α stimulation induced a 5 fold increase in TCF- β -catenin mediated transcription. This could be inhibited by use of an EGF-receptor kinase inhibitor, tyrphostin.

This data has identified that TGF- α , which is up regulated in the majority of human epithelial cancers, may induce tyrosine phosphorylation of β -catenin by receptor-ligand activation. This results in its migration to the nucleus where it can participate in the activation of β -catenin / TCF mediated transcription, the target genes of which