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The 1984 Annual Meeting of the Society was held at the University of Liverpool under the presidency of Dr R B McConnell. One hundred and thirty four oral and 94 poster communications were presented in the scientific sessions; the abstracts of these are printed below.

LIVER
W1–14

W1
Metabolism of mannose-terminated glycoproteins by hepatic sinusoidal cells

J A SUMMERFIELD, M E TAYLOR, AND M S LEANING *(Departments of Medicine and Physics, Royal Free Hospital, London)* Mannose (Man–) terminated glycoproteins are rapidly cleared from the blood by receptors on hepatic sinusoidal cells. In earlier studies using acid precipitation to estimate the catabolism of the glycoproteins, measurement artifacts led to models requiring exocytosis of whole ligand. In these studies the fate of glycoprotein was assessed in rats by measuring radioactivity in blood, liver, bile and other tissues over 40 minutes after an intravenous injection of 57 pmol radioiodinated glycoprotein. Ligand catabolism was measured by gel filtration. With these data a new compartmental model was formulated. The metabolism of ^{125}I–agalactoorosomucoid (^{125}I–AGOR) and ^{125}I–mannose $_{36}$–bovine serum albumin (^{125}I–Man$_{36}$BSA) was studied. Both ligands accumulated principally in liver but more ^{125}I–AGOR (~30%) than ^{125}I–Man$_{36}$BSA (~10%) accumulated in other sites. Uptake parameters indicated that Man$_{36}$BSA (0·78 min) had a higher affinity for the cell receptor than AGOR (0·50 min). Intracellular transport of ligand from the cell membrane to the lysosome was estimated by a transport parameter (Tau) in the model. This was much greater for Man$_{36}$BSA (~3 min) than for AGOR (~0 min). These data may indicate that the rate of receptor–ligand uncoupling of Man$_{36}$BSA is slower than for AGOR. Furthermore, the rate of catabolism of Man$_{36}$BSA (0·27 min) was twice that of AGOR (0·12 min) probably reflecting differences in susceptibility of the protein moieties of the ligands to proteolysis. This model produced a good statistical and graphical fit to both sets of data without the need for exocytosis. The data show that ligands entering the cell by a common receptor may subsequently be processed differently.

W2
Dynamic scintigraphy in cirrhosis

M MCLAREN, J FLEMING, S KARRAN, AND I TAYLOR *(University Surgical Unit, Southampton)* Dynamic hepatic scintigraphy yields information related to haemodynamic and reticuloendothelial function in liver disease by measuring the mesenteric fraction of liver blood flow (M F) and the liver:spleen activity ratio (L:S ratio). It has been used to study 45 patients with liver cirrhosis, 24 of whom had bled from varices. Control data were provided by 30 subjects with normal liver function. For the overall group of cirrhotic patients the median MF was 0·28 compared with a control value of 0·56 ($p<0·001$) and the L:S ratio was 1·5 compared with 4·75 ($p<0·001$). The sensitivity in the diagnosis of cirrhosis was 84% for the MF and 89% for the L:S ratio. This increases to >95% by calculating the geometric mean of MFxL:S ratio. Within the group of patients with cirrhosis the median MF for patients who had gastrointestinal bleeding was 0·22 compared with 0·33 for non-bleeders ($p=0·035$), and the L:S ratio was 0·95 compared with 1·9 ($p=0·003$).

These data indicate a significant reduction in the venous flow to the liver and a significant increase in functional splenomegaly not only in patients with cirrhosis when compared with controls but also between those who have or have not bled from varices. The value of such information lies in diagnosis and monitoring the progression of disease or response to treatment.

W3
Intrahepatic shunting and its relationship to portal pressure and blood flow

M MCLAREN, J FLEMING, S KARRAN, AND I TAYLOR *(University Surgical Unit, Southampton)* It has been suggested that in cirrhosis intrahepatic shunting between all these major blood vessels occurs. The relationship of the degree of shunting to the level of portal pressure is not known but if a manipulation of shunting results in a fall in portal pressure this could have therapeutic implications. A study was undertaken to assess the relationship of portal venous shunting to blood flow and portal pressure.

Cirrhosis, assessed by histological and biochemical criteria, was induced in 45 male Wistar rats by intragastric administration of either carbon tetrachloride (n=25) or dimethlynitrosamine (n=20). Effective liver blood flow (ELBF) and its relative arterial/venous components were measured using Tc99m sulphur colloid, portal pressure was recorded manometrically and the degree of shunting obtained by intraportal injection of Co57 microspheres.

Both portal hypertension (median control 9cm saline, cirrhosis 16·5cm saline $p<0·001$) and shunting (median control 0·3%, cirrhosis 23·0% $p<0·001$) increased significantly in cirrhosis. There was no significant correlation between shunting and either a decrease in ELBF ($r=0·3$) or a decrease in its venous component ($r=0·36$).

There was, however, a significant correlation between the increase in shunting and an increase in portal pressure, $r=0·67$ $p<0.001$. The results do not indicate any direct relationship between the development of shunting and changes in measured flow but intrahepatic portal venous shunt-

ing does increase with rising portal pressure.

W4

Defective sulfoxidation combined with rapid carbon oxidation in the liver may predispose to chlorpromazine jaundice.

E ELIAS, R H WARING, AND S C MITCHELL *(Department of Medicine, QE Hospital Medical School, Birmingham, Department of Biochemistry, University, Birmingham, and the Department of Pharmacology, St Mary's Hospital Medical School, London)*
Chlorpromazine is a major tranquillising agent which is known to be metabolised in man to give both hydroxylated and sulfoxide metabolites. We proposed on the basis of *in vitro* work that rapid conversion of chlorpromazine (CPZ) to hydroxy-metabolites and/or slow metabolism to the relatively non-toxic sulphoxides might be the underlying cause of CPZ hepatotoxicity. This hypothesis was investigated using S-carboxymethyl-cysteine (SCMC) and debrisoquine as probes for *in vivo* sulphur- and carbon oxidation-capacity respectively. Both these drugs are known to show a wide range of metabolism in normal populations. Urinary metabolites and unchanged compound concentrations (0–8 h) were determined after oral SCMC (750 mg) and debrisoquine sulphate (10 mg) in consecutive days in three subjects who had fully recovered from prolonged jaundice after exposure to CPZ (twice in one subject). All three subjects showed very low capacity for sulfoxide formation (Sulfoxidation Index (SI) of 32, 35, and 80). These values are at the extreme end of the range found in a normal population. None of the patients possessed an impaired debrisoquine oxidation capacity (debrisoquine Metabolic Ratio (MR) 0.3, 3·6, and 0·6). All three CPZ-toxicity patients therefore had high SI/MR values, and we suggest that the combination of relatively defective sulfoxidation and extensive carbon-oxidation capacity may predispose to CPZ jaundice.

W5

Effects of de-amino 8 D arginine vasopressin (DDVAP) on haemostasis in patients with liver disease

A K BURROUGHS, K MATTHEWS, D KELLY, M QADIRI, T TUDDENHAM, AND N McINTYRE *(Department of Medicine and Haemophilia, Royal Free Hospital School of Medicine, London)* DDVAP shortens bleeding time in normal subjects, haemophiliac and von Willebrand patients, mainly by raising the concentration of all components of factor VIII complex. DDVAP, however, also shortens bleeding time in uraemics, and is used for prophylaxis and treatment of bleeding, despite already raised factor VIII concentrations. The latter is also seen in cirrhotics, but the effects of DDVAP in such patients is not well reported. We have studied the effect of a 15 minute intravenous infusion of 0·3μg/kg DDVAP at one and three hours post infusion as compared with baseline values of prothrombin, partial thromboplastin (PTTK), thrombin and bleeding times factors VII, IX, X, XI, XII, VIIIC, VIIIRAG, VIIIR-Cof, fibrinogen, fibrin monomers (FM) and degradation products (FDP), euglobulin lysis time and fibrin plate assay. Results to date are for six patients: five with parenchymal liver disease (prothrombin ratio of 1·3 or more) and one patient with non-malignant obstructive jaundice. All were vit K replete. Abnormal and normal bleeding times were shortened by about 30% at both one and three hours. At the same time PTTK was shortened to within the normal range, and increases above baseline concentrations were seen for factors VIIIC by 26-106 IU/1, VIIIRAG by 50-95IU/1 and VIIIRiCof by 80-120IU/1. There were also increases in factors XI and XII. There was no change in other factors, prothrombin time, fibrinogen, FM, or FDP. No side effects were encountered. The reduction in bleeding time is probably because of increases in the components of factor VIII complex. Equivalent increases would only be seen following large volumes (2-3 1) of fresh frozen plasma. Thus DDVAP may be very useful as adjuvant therapy in the prophylaxis and treatment of bleeding in cirrhosis. Clinical evaluation and further studies on haemostasis are needed.

W6

Oral H_2 – receptor antagonists do not acutely alter liver blood flow

J CRAMPTON, M STAPLETON, G DAVIES, AND I T GILMORE *(Gastroenterology Unit, Broadgreen Hospital, Liverpool)* There have been conflicting reports of the effect of H_2 receptors on liver blood flow. The issue is of some clinical importance because of potential effects on drug metabolism and portal pressure. Interpretation of previous studies has been difficult because only a single anion, indocyanine green (ICG), has been used and its clearance often equated with liver blood flow. The present study examines the simultaneous pharmacokinetics of two separate anions ICG and ^{14}C-glycocholate. Extraction ratios were estimated by analysis of the biexponential plasma disappearance curves and liver blood flow calculated.

Ten healthy volunteers fasted and received a single oral dose of cimetidine 400 mg, ranitidine 150 mg or placebo in random order on three occasions one week apart. Two hours later clearances measured for ICG (ml/min/kg) were: cimetidine, 6·9± 2·9; ranitidine, 7·9±3·1; placebo, 7·1±1·6; and for ^{14}C-glycocholate: cimetidine, 8·4± 2.3; ranitidine, 8·1±2·2; and placebo, 8·6± 1·9. Similarly there was no difference in the calculated extraction ratios or liver blood flow.

Using the same technique, it has recently been suggested that cimetidine but not ranitidine may reduce liver blood flow after chronic administration secondary to inhibition of enzyme activity and reduction of intrinsic clearance. The lack of effect of a single dose of cimetidine on liver blood flow would be compatible with this hypothesis as in this study neither H_2 receptor antagonist caused significant alteration of liver blood flow in normal subjects.

W7

Hepatobiliary fibrocystic diseases

J A SUMMERFIELD, J CADAFALCH, AND S SHERLOCK *(Academic Department of Medicine, Royal Free Hospital, Pond Street, London)*
Cystic lesions of the liver and bile ducts are being increasingly recognised with improved diagnostic techniques. We have reviewed 49 patients diagnosed between 1966-1984. They had congenital hepatic fibrosis (CHF) 14, CHF and Caroli's disease (CD) 12, CD 8, polycystic liver (PC) 11, microhamartoma (MH) 10, and choledochal cyst (CC) 3. Three patients (27%) with PC also had MH. Six patients (24%) with PC, MH or CC also had CHF or CD. The presentation age of CHF (7±3 years: mean±SEM) was younger than CHF and CD (15±4 years) or CD (37±9 years). Polycystic liver (37±6 years) and MH (50± 6 years) presented later. Most CHF and CD (83%) and CD (75%) were male. Congenital hepatic fibrosis presented with variceal haemorrhage (4) and/or hepatosplenomegaly (13). Congenital hepatic fibrosis and CD patients presented with variceal haemorrhage (3), hepatosplenomegaly (10) or cholangitis (2). Caroli's disease patients presented with cholangitis (5) and/or

hepatosplenomegaly (6). Variceal haemorrhage began earlier (14±3 years) than cholangitis (36±5 years). Polycystic liver and MH presented with incidental liver disease or abdominal pain. Portal hypertension developed in most patients with CHF (12/14) and CHF and CD (7/10), but in no patient with CD. Cholangitis developed in 8/10 with CHF and CD and 6/7 CD. Five patients with CHF and CD first developed variceal haemorrhage and 10±3 years later began to have cholangitis. Polycystic kidneys were most frequent in CHF (9/14) but were also found in other groups. In conclusion (1) more than one fibrocystic disease and polycystic kidneys were usually found in a patient, (2) CHF and CD divided into three groups: CHF and CD alone or CHF and CD. Most CD were male. Congenital hepatic fibrosis had variceal haemorrhage, CD had cholangitis, CHF and CD had first haemorrhage and later cholangitis.

W8

Low serum androgens in primary hepatocellular carcinoma

M JAWED IQBAL, T P CORBISHLEY, M L WILKINSON, J KEATING, AND ROGER WILLIAMS *(Liver Unit, King's College Hospital and School of Medicine and Dentistry, Denmark Hill, London)* The importance of androgens in hepatocellular carcinoma (HCC) has been shown in previous studies from this unit in which androgen receptors were detected in HCC tissue but not in normal or cirrhotic liver tissue and in a further study showing an alteration in the characterisation of binding of circulating sex-steroid coincident with the development of HCC in patients with primary biliary cirrhosis (PBC). In the current study total serum testosterone (T), 5 -dihydrotestosterone (DHT) and oestradiol-17 (E2) lends (radioimmunoassay) and sex hormone binding globulin (SHBG) levels (two-tier column assay) were determined in 20 male patients with both cirrhosis and HCC and the results compared with those in age-matched groups with alcoholic cirrhosis (AC) and PCB and with normal controls. Serum T (2·6 ± SD., 2·70 nmol/l), DHT (0·51±0–305 nmol/l) and E2 (83·1±99·80 pmol/l) levels were lower in the HCC patients than in either cirrhotic group and the levels of the two androgens were also lower than those in normals. Sex hormone binding globulin (96±42·1 nmol DHT bound/l) levels were higher than in normal controls but not significantly different from those in the two cirrhotic groups. Peripheral conversion is an important source of E_2 and DHT in men, and the low levels of all three steroids measured in the current study in patients with HCC are consistent with reduced substrate (T) availability. Low levels of T, a feature we have found in other malignancies, may be due to impaired testicular production and/or pituitary/hypothalmic dysfunction.

W9

Mitoxantrone as single agent therapy in primary hepatocellular carcinoma

A A DUNK, S C SCOTT, P J JOHNSON, I MURRAY-LYON, R WILLIAMS, AND H C THOMAS *(Royal Free Hospital, Cyanamid International Research Centre, Kings College Hospital, Charing Cross Hospital, London)* Forty patients with primary hepatocellular carcinoma (PHC) were treated with Mitoxantrone, an anthracenedione structurally similar to Adriamycin. Thirty five of these patients had received no previous form of therapy. The drug was given intravenously at a dose of 12 mg/m^2 once every 21 days. Dosage could be modified by 2 mg/m^2 increments depending on toxicity and tolerance. All patients were considered evaluable for toxicity/tolerance analysis and at the time of reporting, 22 patients were considered evaluable for response analysis. Based on a modification of the UICC criteria, one patient achieved a complete remission of 13 weeks duration. To date, five patients have achieved partial remission, the longest being of 21 weeks duration. The overall response rate is 27%. A further four patients remained in the UICC 'No change' category, the longest for 42 weeks.

The drug was well tolerated. Nausea occurred in 23% of cycles and vomiting occurred in only one patient. Alopecia occurred in one patient and other adverse effects were rare. Leucopenia was dose-limiting and a white cell count of < 1000/mm^3 occurred on three occasions. Thrombocytopenia occurred but was not a clinical problem. A platelet count of < 40 000/mm^3 occurred twice. Haematological toxicity was easily managed by dosage adjustment. Cardiac events occurred in three patients (two cases of atrial arrythmias, one case of asymptomatic diminution in cardiac function revealed by radionuclide ventriculography). Two of these patients had received > 13 cycles of therapy.

Mitoxantrone shows activity in PHC, similar to that seen with Adriamycin, but with significantly less acute toxicity. Its chronic toxicity profile remains to be evaluated.

W10

Metabolic bone disease in PBC - high bone turnover, not osteomalacia

H C MITCHISON, A J MALCOM, M F BASSENDINE, AND O F W JAMES *(Department of Medicine, Freeman Hospital, Newcastle upon Tyne and Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne)* The nature and incidence of metabolic bone disease in PBC is still controversial. Bone biopsy with tetracycline label is the best method of assessment.

We examined 13 women with PBC who had received no treatment likely to influence bone status. Five had cirrhosis, eight had Stage III features on histology, three were premenopausal, 10 postmenopausal, 12 were symptomatic of liver disease, none of bone disease, four had bilirubin >50 m/l for >6 months. Photon absorbtiometry of femur and forearm and right iliac crest bone biopsy after double tetracycline label were carried out in each patient, together with a C-14 triolene breath test to look for fat malabsorbtion.

The photon absorbtiometry showed a wide scatter of values but not outside those of an age-matched control population, results did not correlate with other variables. The bone biopsies showed no evidence of osteoporosis beyond that expected for age and sex. The percentage of trabecular bone with osteoid was within normal limits but the osteoid seams were wide (osteoid volume 2·48%±0·5, normal 1·9%± 0·4). This hyperosteoidosis, however, was associated with high normal appositional rate of 1 mm/day average which is not compatible with osteomalacia. Four patients had abnormal triolene breath tests but this did not correlate with clinical or histological status or bone results.

In conclusion, we found neither osteoporosis or osteomalacia on biopsy. We suggest that previous reports of osteomalacia in PBC have been because of interpretation of wide osteoid seams in the absence of information about the appositional rate (only obtainable after double oxytatracycline label). Our findings are compatible with a high rate of bone turnover; they raise no contraindications to a therapeutic trial of prednisolone in these patients.

W11

Familial IgM rise in PBC

D R TRIGER AND R J MUGGLETON *(Department of Medicine, Royal Hallamshire Hospital, Sheffield)* In a study to examine possible genetic and environmental factors in primary biliary cirrhosis, we have studied the clinical, biochemical, and serological features in 200 relatives of 44 patients with this condition (spouses and their first degree relatives 63, siblings 72, children 65). Positive antimitochondrial antibody (titre equal or greater than 1:20) was found in only three cases (all female siblings) and clinical evidence of PBC was present in only one. A significant rise in mean IgM levels was seen in the female siblings (2·4 g/l *vs* 1·67 g/l $p>0·05$) as well as in the daughters (2·40 g/l *vs* 1·88 g/l $p>0·05$) of PBC compared with age and sex matched controls. These differences were largely accounted for by clustering of high IgM levels in eight of these families. No difference was found in IgM levels in male relatives compared with controls. There was no difference in serum IgG, IgA or routine biochemical values between any of the groups of relatives and controls. In conclusion elevated IgM in PBC appears to occur independent of the clinical disorder. The pattern of family clustering does not correspond to any recognised mode of inheritance but the data are consistent with an environmental factor playing at least some contributory role. This factor may be relevant to the pathogenesis of PBC.

W12
Modified Sugiura procedure versus portosystemic shunt operations for portal hyper tension and variceal bleeding – prospective study

G M ABOUNA, A T MENKARIOUS, H BAISSONI, AND O F Y OMAR *(Department of Organ Transplantation Surgery, Faculty of Medical and Mubarak Al-Kabeer Hospital, Kuwait University, Kuwait)* The surgical treatment of bleeding oesophageal varices remains controversial. A prospective study involving 48 patients with variceal bleeding was carried out in order to compare the results of a modified Sugiura operation with those of shunting procedure. In this modification a transabdominal, one-stage operation, a highly selective vagotomy without pyloroplasty is performed and a stapling machine used for oesophageal transaction. After the source of bleeding is determined by endoscopy, patient resuscitation is continued with blood transfusions, Pitressin and oesophageal tamponade. The study comprised three groups of patients: In group I (n=10) an emergency mesocaval shunt was carried out because of continuing haemorrhage despite resuscitation and sclerotherapy, in some cases. In group II (n=14), an elective shunt procedure was carried out (12 distal splenorenal and two mesocaval). In group III a modified Sugiura operation was carried out electively in 22 and as an emergency in two. The age, sex, Child's grading and the pathological causes of portal hypertension were comparable among the groups. All patients but one were non-alcoholic. Patients were evaluated at 4–55 months after treatment. In the patients of group I, the operative mortality was 20%, recurrent haemorrhage 40%, shunt occlusion 20%, encephalopathy 20%, late death 20% and patient survival 60%. In group II, the operative mortality was 14·3%, recurrent bleeding 14·3%, encephalopathy 7%, late death 7% and patient survival 85·7%. In group III, operative mortality was 5%, recurrent bleeding 5%, no encephalopathy, no late deaths and patient survival 95%. It is concluded that a modified Sugiura non-shunt operation is an effective procedure in arresting variceal haemorrhage, it has low operative mortality, increased patient survival and no encephalopathy.

W13
Effect of a selective B_2-blocker on hepatic haemodynamics in the cirrhotic rat

S A JENKINS, J JOHNSON, J N BAXTER, P DEVITT, AND R SHIELDS *(Department of Surgery, University of Liverpool, Liverpool)* Although propranolol may be effective in reducing the rate of rebleeding from oesophageal varices, $ß_1$-blockade sometimes makes resuscitation difficult should the patient experience recurrent variceal haemorrhage. This study was therefore carried out to investigate the effects of systemic and intraportal administration of a selective $ß_2$-blocker (ICI 118,551) on hepatic haemodynamics in the cirrhotic rat.

Rats made cirrhotic with dimethynitrosamine received systemic infusions of 0, 2, 4, or 8 mg $ß_2$-blocker/kg body wt/min. Portal pressure (PP), portal venous flow (PVF), arterial blood pressure (BP) and liver blood flow (LBF) were measured before and after the infusion of the $ß_2$-blocker. Similar measurements were made before and after intraportal bolus injection of the $ß_2$-blocker.

The systemic infusion of 10 ug/kg body wt/min $ß_2$-blocker reduced PP (15·4±1·0 to 13·0±0·9 mmHg), PVF (17·2±2·2 to 10·6± 1 ml/min) and LBF (25·2±2·0 to 19·3±1·6 ml/min/100g) significantly ($p<0·05$; Student's paired *t* test) without influencing heart rate or BP. An intraportal injection of $ß_2$-blocker resulted in an immediate but transient fall in PP (12·4±0·48 to 10·3±0·41 mmHg; $p< 0·05$).

These results suggest that (a) a selective $ß_2$-blocker (ICI 118,551) can modify hepatic haemodynamics without a significant effect on the systemic circulation, and (b) an intraportal $ß_2$-blocker may be of value in the control of bleeding oesphageal varices.

W14
Effect of bile duct ligation on hepatic glutathione S-transferase activity and bile acid binding capacity

P R BAKER AND Y SIOW *(University Department of Surgery, Ninewells Hospital and Medical School, Dundee)* Glutathione S-transferases (GST), a group of detoxification enzymes, are also believed to play a role in the intracellular binding and hepatic transport of bile acids. As bile acids inhibit these enzymes, however, other cytosolic proteins may be involved, particularly in large duct obstruction where bile acids accumulate in the liver. To investigate this, GST activity on 1-chloro-2,4 -dinitrobenzene and protein binding of 14C – bile acids (ultra filtration method) were studied in hepatic cytosol (100 000 g supernatant) prepared from rats one week after a sham(SH) procedure, and one (BDL1) and four (BDL4) weeks after ligation and division of the common bile duct (n=6 per group). Glutathione S-transferases activity (mmol/min/kg body weight) in cytosol diafiltered to remove inhibitors such as bile acids was progressively and significantly (Student's *t* test) decreased in BDL1 (2·5±0·3 (SD), $p<0·005$) and BDL4 (1·7±0·5 $p<0·001$) rats compared with SH rats (3·5±0·4). Bile acid binding capacities of hepatic cytosolic proteins (μmol/kg body weight) remained at control levels in BDL1 rats. In BDL4 rats, however, although there was little change in glycocholic acid and cholic acid binding, significant increases in the binding capacities compared with BDL1 animals was observed for chenodeoxycholic acid (19·8±6·5 (SD), and 28·6±6·7, $p<0·05$) and lithocholic acid (65·8±16·5 and 119·5± 22·5, $p<0·001$). After fractionation of pooled cytosol on an affinity chromatography gel, proteins eluted with 10 mM taurochenodeoxycholic acid or 3M sodium thiocyanate exhibited the highest bile acid binding but negligible GST levels. This study has shown that large duct obstruction

causes depletion of important detoxification enzymes. The enhanced cytosolic protein binding capacities for the more toxic bile acids, however, may represent a compensatory protective mechanism which is induced by prolonged cholestasis.

LIVER
T1-12

T1
Monocyte suppression in cirrhosis

UNA McKEEVER, N P KENNEDY, D G WEIR, AND C FEIGHERY *(Department of Immunology and Clinical Medicine, Trinity College and St. James' Hospital, Dublin, Eire)* We recently described the presence of monocytosis in patients with severe alcoholic liver disease (ALD). In the present study, the functional significance of this monocyte excess was investigated.

Nineteen patients were studied: twelve with severe ALD; five with chronic active hepatitis (CAH); two with primary biliary cirrhosis (PBC). Twelve patients had an established cirrhosis: ALD (seven), CAH (three) and PBC (two). Nineteen healthy age-matched subjects served as controls. Monocytes in the peripheral blood mononuclear cell (PBMC) population were enumerated using the monoclonal antibody MO-2. Monocyte mediated suppression of PHA induced PBMC proliferation was assessed by incorporating indomethiacin (a prostaglandin synthetase inhibitor) into the culture system.

The Wilcoxson's rank sum test and the Student's t test were used in statistical analysis. The results (mean ± SD) showed that patients with ALD had a significantly higher percent monocyte count (28.3±8.9, $p<0.01$) than controls (18.1±6.7) confirming our earlier findings. Although monocyte mediated per cent suppression in the ALD group was greater (20·1±28·0) than the controls (3·9±16·7), this difference was not statistically significant. When patients with cirrhosis were studied as a group a significant monocytosis (28·7± 8·1%, $p<0.01$) and monocyte mediated per cent suppression (39·6±23·1, $p<0·02$) was observed.

In conclusion, monocytosis appears to be a feature of chronic liver disease of diverse aetiology and, in patients with cirrhosis, results in significant *in vitro*, prostaglandin dependent, immunosuppression.

T2
Albendazole treatment of hydatid disease in an animal model

D L MORRIS, M F STALLBAUMER, M J CLARKSON, J PRITCHARD, AND J CHINNERY *(Department of Surgery, University Hospital, Nottingham, Department of Veterinary Preventative Medicine, University of Liverpool, Liverpool)* Despite encouraging clinical and radiographic results of albendazole treatment of human hydatid disease neither constitute absolute proof of an therapeutic action.

Seventeen sheep with active naturally occurring pulmonary hydatid disease were identified radiographically. Six were treated with albendazole (three at 10 mg/kg and three at 20 mg/kg) for six weeks before necropsy examination. Viability of protoscolices was assessed by needle puncture, vital staining and warm microscopy. The remaining sheep underwent thoracotomy and needle puncture so that viability could be confirmed before therapy. There was one postoperative death, one hydatid proved to be non-viable, of the remainder seven were treated at 10 mg/kg and two at 20 mg/kg for six weeks. Several sheep developed leucopaenia which led to septicaemia and death in two animals. At postmortem examination all cysts were flaccid, and contained little fluid which was straw coloured instead of clear. The laminated and germinal membranes had often fallen away from the ectocyst. Viability testing showed that all protoscolices were dead. In addition electron microscopy showed the germinal membrane to be completely disorganised and degenerate. In order to confirm that thoracotomy alone has no detrimental effect on viability one sheep underwent thoractomy, conformation of viability and at necropsy six weeks later the parasite was still alive. We conclude that six weeks treatment with albendazole 10 mg/kg kills protoscolices within viable hydatid cysts in sheep, but significant leucopaenia has been seen.

T3
New biochemical criteria for hepatic transplantation versus drug therapy in primary biliary cirrhosis (PBC)

B P O'NEILL, A SMITH, N Y HABOUBI, F I LEE, AND T W WARNES *(Liver Section, University Department of Gastroenterology, Manchester Royal Infirmary, Department of Medicine, Victoria Hospital, Blackpool)* Our aim in this study is to investigate by conventional and dynamic liver function tests (LFT's) the pathophysiological defects in 47 PBC patients and in a subgroup dying within 18 months.

Serum bilirubin, albumin, prothrombin index (PI), galactose elimination capacity (GEC) (hepatic functional cell mass) and BSP-k_2 (hepatic excretory capacity) were measured. Analysis was by Fisher's exact test. Group A consisted of 29 patients surviving longer than 18 months and group B of 18 patients surviving less than 18 months.

The results show that serum bilirubin was abnormal in 31% of group A and in 83.3% of group B ($p=0.00055$). Serum albumin was abnormal in 10.3% of group A and in 61.1% of group B ($p=0.00036$). Prothrombin index was abnormal in 11.5% of group A and in 35·7% of group B ($p=0.082$). Galactose elimination capacity was abnormal in 65·2% of group A and in 93·8% of group B ($p=0·041$). BSP-k_2 was abnormal in 58·3% of group A and in 100% of group B ($p=0·00231$).

We conclude that in the group as a whole, the conventional LFT's were abnormal in 57.4%, while dynamic LFT's were abnormal in 92.3%. BSP-k_2 was the earliest and most consistent defect in PBC. Dynamic LFT's are therefore the preferred method of monitoring response to drug treatment in early disease. In most patients serum albumin and bilirubin became abnormal only in the late stages and 17% of our patients had a normal bilirubin within 18 months of death. All tests combined gave a predictive index for death within 18 months of 78%. Prediction of death was improved significantly by determination of GEC and BSP-k_2 and these tests should be performed in all patients in whom liver transplant might be considered.

T4
Use of a prognostic index in assessment of outcome of liver transplantation in patients with primary biliary cirrhosis

J NEUBERGER, E CHRISTENSEN, D G ALTMAN, N TYGSTRUP, AND ROGER WILLIAMS *(The Liver Unit, King's College Hospital and School of Medicine & Dentistry SE5 and Department of Hepatology, Hvidovre Hospital, Copenhagen, and CRC Northwick Park Hospital, Middx)* Primary biliary cirrhosis (PBC) is one of the commonest parenchymal liver diseases currently being treated by liver transplantation in the Addenbrookes/King's College Hospital programme, but difficulties arise in choosing the optimal time for surgery. Currently,

a transplant is offered when disability is severe and when the anticipated survival time is less than one year. The present study was based on a prognostic index to compare the observed survival after grafting with estimated survival. The index was derived from analysis of 216 patients participating in an international therapeutic trial in PBC, using the Cox regression model for censored survival. Factors of prognostic significance included age, serum bilirubin and albumin, histological finding of cirrhosis and central cholestasis. The index was transformed to give a median survival time.

Retrospective analysis using the model showed the estimated median survival time of the grafted patients was four months and in only four was greater than one year although less than 21 months in all. After grafting, five lived with survival periods of 18 to 84 months and three are alive and well over three years later. By life table analysis, the observed survival was significantly greater than the estimated time ($p<0.01$). Perioperative mortality, however, was high, with 13 patients dying within six weeks because of surgical, infective, and graft problems. This model may be of value in selecting the optimal timing of transplantation and further prospective evaluation is required to identify those factors determining a satisfactory outcome of liver transplantation.

T5

Interim results show major improvement in survival in pre-icteric Indian childhood cirrhosis (ICC) treated with D-penicillamine (DMC).

M S TANNER, D G SIDHAYE, S A BHAVE AND A M PRADHAN *(Department Child Health, University of Leicester, Leicester, UK, and Department Pediatrics, KEM Hospital, Poona, India)* Untreated, 43 of 58 children with ICC died within eight weeks (1980). d-Penicillamine in advanced cases insignificantly improved survival (1980-81). d-Penicillamine 20 mg/kg/day (Group A), DMC + prednisolone 2 mg/kg/day for four weeks then 5 mg/kg/day (Group B), or placebo tablets (Group P), was given to 24 earlier cases of ICC without ascites or jaundice. Thirteen were allocated to treatment groups in rotation (1982). Eleven entered a double blind study with code breaking after three months (1982).

Results to February 1984: show 8/8 in Group P died after 41±31 (12-109) days. 4/8 in Group A and 3/8 in Group B died after 132±148 (35-448) days. 9/16 in Group A and B are well after 15.8±6.4 (6-25) months. Analysis of entry parameters indicate a marginal Group P disadvantage, preventing trial discontinuation. In biopsies of survivors after six months, orcein staining was scanty or absent; three showed inactive micronodular cirrhosis, and two were normal.

T6

D-penicillamine in primary biliary cirrhosis (PBC) – an untested (and untestable?) treatment

O EPSTEIN, D G COOK, S JAIN, AND SHEILA SHERLOCK *(Academic Department of Medicine, Royal Free Hospital School of Medicine, London)* Since 1973, 98 PBC patients have been enrolled into a randomised controlled trial of penicillamine. On entry to the study, the prognostic profiles of the penicillamine and placebo treated groups were similar. Because of expected drug side effects, the randomisation was weighted to allow a 3:2 ratio of penicillamine to placebo treated patients. Over a mean follow-up of 66 months death occurred in 16 of 37 placebo treated patients (43%) and 18 of 61 penicillamine treated patients (30%). This difference in survival, although favouring the penicillamine group does not achieve statistical significance when analysed by the log rank test ($p=0.08$). This result differs from a previous published analysis of 87 patients followed for a mean of 45 months, which indicated significantly improved survival in penicillamine treated patients ($p<0.01$). To determine whether the changing significance level reflects inadequate sample size, we calculated the size of penicillamine trial necessary to detect a real reduction in five year mortality from 40% to 30%, with 80% certainty, at the 5% significance level. To achieve this goal, 710 patients would be required to participate in the study. Neither this study, nor any other published penicillamine trial has been designed to accommodate the possibility of type II error. Future design of clinical trials in PBC must appreciate the scale of trial required to test the treatment effect.

Despite 10 years of clinical evaluation, the effect of penicillamine on survival remains uncertain. The trend in our trial remains encouraging, but unless long-term collaborative multicentre trials are mounted, this, and any other treatment, will remain untested.

T7

Controlled trial of acyclovir in chronic HBsAg, HBeAg positive carriers

G J M ALEXANDER, J E HEGARTY, E FAGAN, P GUARASCIO, A L W F EDDLESTON, AND ROGER WILLIAMS *(The Liver Unit, King's College Hospital and School of Medicine and Dentistry Denmark Hill, London)* Clinical and histological improvement usually follow spontaneous loss of ciral replication in chronic HBsAg carriers – the basis of antiviral therapy. To date, no anti-viral agent has unequivocally been shown to increase the natural rate of seroconversion.

To assess its antiviral properties, a randomised controlled trial of acyclovir, 45 mg/kg by continuous infusion for 28 days, *versus* no treatment, has been performed in 30 patients positive for HBsAg and HBeAg for a minimum of six months. Patients were stratified for sex, histology (minimal liver damage, chronic persistent hepatitis or chronic active hepatitis) and homosexual activity.

At the end of the treatment period, serum DNAp activity, initially positive in 13 of the 15 patients, had fallen in nine, inhibition exceeding 50% in two patients. Side effects were minimal (transient haematuria one, dry skin 14). No adverse effect on renal function was observed.

After 12 months' follow up, four of 14 of the treated group and two of 13 of the untreated group had seroconverted to anti-HBe; one of those treated had also developed anti-HBs. One further patient in each group had become DNAp negative, but remained HBeAg positive. Seroconversion was unrelated to histology, duration of disease or homosexuality.

The results of this study indicated that acyclovir partially inhibits viral replication in HBsAg positive patients but that this effect is not accompanied by a significantly increased rate of seroconversion.

T8

Effect of propranolol treatment on salt and water homeostasis

P C HAYES, M K FENWICK, AND I A D BOUCHIER *(University Department of Medicine, Ninewells Hospital and Medical School, Dundee, Scotland)* The effect of chronic administration of long acting propranolol on body weight, skinfold thickness, and urinary sodium excretion was measured at 0, six and 12 months in 15 patients with chronic liver disease in double

blind, placebo controlled fashion. Total body exchangeable sodium and total body water (TBW) was also measured using [^{24}NA] sodium and tritiated water.

Patients taking propranolol showed a weight gain of 6·65±4.74 kg at 12 months which was significantly greater than in controls 1·04±3·2 kg ($p<0·05$), largely because of an increase in body fat, as determined by skinfold thickness which increased by 17·6± 13·6 mm compared with a fall of 0·5±6·7 mm control subjects ($p<0·05$). Body fat (% of body weight) in patients increased by 3·6% *vs* −0·02% in controls ($p<0·05$).

Urinary sodium excretion increased by 49±52 mmol/l after one year compared with a decrease of 7±37 mmol/l in controls ($p<0·05$). Total body water in patients taking propranolol fell from 39·6±4·7 to 35·0± 4·9 L ($p<0·01$) at six months compared with control values (35·4±10·2 to 33·9±10·1 L) ($p<0·1$) despite the weight gain. This fall in TBW with propranolol therapy was more marked after correction for body weight. After 12 months the total body exchangeable sodium decreased in subjects taking propranolol (2722±373 to 2719±297, $p<0·5$), compared with a significant increase in control subjects (2825±507 to 3043±499 mmol) ($p<0·05$).

We conclude that propranolol reduced the tendency to retain sodium and water in hepatic disease by increasing sodium excretion and increased body weight due to deposition of fat which may represent restoration of lost tissue mass in patients with liver disease.

T9

Recurrence of varices after initial obliteration by sclerotherapy

D WESTABY, B R D MACDOUGALL, AND ROGER WILLIAMS *(The Liver Unit, King's College Hospital and School of Medicine and Dentistry, Denmark Hill, London)* To determine the incidence and significance of recurrence of varices after obliteration by sclerotherapy, 147 patients (99 cirrhosis, 48 non-cirrhosis) were prospectively followed for periods up to six years after initial obliteration had been achieved. Routine endoscopic examinations were undertaken at intervals of three to four months for the first year and six monthly thereafter. 'New' varices developed in 99 cases (67%) although these were the cause of bleeding in only 28 patients of whom three died. Twenty five of the 28 patients rebleeding did so within 12 months of initial obliteration of varices. A median of two courses of sclerotherapy (range 1–4) were required to again achieve obliteration. In 20 patients a second recurrence of varices occurred with bleeding in eight cases but no associated deaths. There was no correlation between the aetiology of cirrhosis or the severity of the underlying liver disease and the development of 'new' varices. The high rate of recurrence of varices applied equally to those with a portal vein thrombosis.

The results indicate that recurrence of varices can be expected in the majority of patients after initial obliteration by sclerotherapy. The frequency of bleeding, however, may be minimised by regular follow up endoscopy, and injection of 'new' varices, particularly during the first 12 month period.

T10

Can propranolol prevent recurrent variceal bleeding in the period before obliteration of varices by injection sclerotherapy?

D WESTABY, W MELIA, J HEGARTY, A GIMSON, A STELLON, AND ROGER WILLIAMS *(The Liver Unit, King's College Hospital and School of Medicine and Dentistry, Denmark Hill, London)* Recurrent variceal bleeding occurs in up to 40% of patients during injection sclerotherapy in the period before obliteration of varices. As long term B receptor blockade has been shown to reduce the frequency of recurrent variceal haemorrhage, the present study was designed to assess the effect of propranolol in the prevention of such bleeding in the preobliteration period.

The 53 patients (44 cirrhosis, nine non-cirrhosis) presenting with variceal bleeding were randomised after haemodynamic stabilisation to undergo sclerotherapy alone or, in addition, to receive propranolol in a dose sufficient to reduce resting pulse rate by 25%. Sclerotherapy was carried out using the sheath technique and repeated at weekly intervals until the varices were obliterated.

A median of four courses of sclerotherapy were required in each group to obliterate the varices. Eight of the 27 patients undergoing sclerotherapy alone rebled in the period before obliteration with a total of 11 episodes compared with seven of the 26 patients receiving combined treatment with 13 episodes ($p>0·9$). Two patients in each group died of varieceal haemorrhage. Propranolol precipitated encephalopathy in one patient and complicated resuscitation after bleeding in a second.

The results of this study indicates that propranolol is ineffective in reducing the frequency of recurrent variceal haemorrhage in the pre-obliteration phase of injection sclerotherapy.

T11

Non-invasive endoscopic measurement of oesophageal variceal pressure: effect of somatostatin

D CLEMENTS, J M RHODES, AND E ELIAS *(Department of Medicine, Queen Elizabeth Hospital, Birmingham)* The efficacy of somatostatin in the treatment of oesophageal variceal haemorrhage and its effect on portal pressure are currently unclear, some authors reporting favourable responses and others not. There have been no studies on the effect of somatostatin on non-cirrhotic portal hypertension.

We have studied its effect on variceal pressure using a non-invasive endoscopic pneumatic gauge in five patients (two cirrhotics, three with non-cirrhotic portal hypertension) given a 250 ug iv bolus of somatostatin (Serono). All had previously had at least one documented variceal bleed. Under iv midazolam sedation the variceal pressure was measured before and continuously for 15 minutes after a bolus of somatostatin given over 30 seconds intravenously. Pulse and blood pressure were measured at two minute intervals throughout.

Mean variceal pressure before somatostatin was 40 cm water (range 27-54) and all patients showed a reduction after the somatostatin. The maximum fall in pressure averaged 16 cm water (range 5-34), representing a 37% drop (18·5-71%) occurring seven minutes (range 2-10) after the bolus. There was no significant change in the BP or pulse during the studies and no adverse reactions.

All the patients, regardless of the aetiology of the portal hypertension, showed a significant reduction in their variceal pressure after a single bolus of somatostatin without any major change in their systemic haemodynamics. These results suggest that somatostatin may well be useful in the treatment of acute variceal haemorrhage.

T12

Does compression of varices after endoscopic sclerosis improve the likelihood of obliteration?

J M RHODES, J DAWSON, R COCKEL, P HAWKER,

P DYKES, G V H BRADBY, P HILLENBRAND AND E ELIAS *(Departments of Medicine, Queen Elizabeth, Selly Oak and General Hospitals, Birmingham, Sandwell Hospital and Good Hope Hospital, Sutton Coldfield)* A trial was conducted to determine whether use of the Williams overtube followed by Sengstaken balloon compression of oesophgal varices increases the likelihood of variceal obliteration after sclerotherapy. Forty patients bleeding from previously untreated oesophageal varices were randomised to have their first sclerotherapy by one of two techniques; in 19 patients fibreoscopic injection of the varices was performed under general anaesthetic using a Williams overtube and a Sengstaken balloon was then inserted and the oesophageal balloon inflated to 40 mmHg overnight; in 21 patients varices were injected under iv sedation using a 'free' technique without the overtube or Sengstaken tamponade. Subsequent scleroses in all patients were performed at three to four week intervals using the 'free' technique. Five per cent ethanolamine oleate was used as sclerosant with intention to inject intravariceally. In none of 19 Sengstaken-treated patients and only one of 21 'free' injected patients were the varices eradicated by the first treatment. In a median follow up of 12 months five of 19 (26%) Sengstaken treated patients died and five had non-fatal bleeds while six of 21 (29%) 'free' treated patients died and six had non-fatal bleeds. Varices have so far been completely obliterated in five of 19 Sengstaken treated patients (median number of scleroses required = five) and in six of 21 'free' treated patients (median number of scleroses = four). Two of the Sengstaken treated patients died as a direct consequence of the sclerotherapy, one from oesophageal perforation and one from inhalational pneumonia.

Compression of varices by Sengstaken tamponade after injection of sclerosant does not increase the likelihood of variceal obliteration and may be associated with an increased risk of complication.

GASTRODUODENAL
T13-26

T13
Gastric mucosa cell damage caused by four acetylsaliclic acid preparations and three strengths of alcohol

H J HAGEL, M MELCHNER, G KACHEL, H RUPPIN, W DOMSCHKE, AND D N CROFT *(University of Erlangen-Nuremberg, Federal Republic of West Germany and St. Thomas' Hospital, London)* The mechanism whereby aspirin and alcohol damage gastric mucosa is controversial, one possibility being an acute toxic effect on gastric surface epithelial cells leading to their exfoliation. Instillation of soluble aspirin into the human stomach has been shown to cause exfoliation of surface epithelial cells which has been quantitated by measuring DNA (or cell) loss from the gastric mucosa. In order to further investigate the acute effect of chemical insults to the human stomach the gastric DNA loss technique has been used on seven healthy volunteers to test two strengths of soluble aspirin, a microencapsulated aspirin, a bicarbonate-ascorbic acid formation of aspirin and three strengths of alcohol. In each study three instillations of one of the seven preparations was followed by two saline washings after each instillation. All seven preparations were studied at weekly intervals in the seven volunteers. Instillations of 0·5 g and 1·0 g soluble aspirin caused significant ($p<0·10$) increases of greater than 150% above basal gastric DNA loss rates and the loss was dose dependent. Microencapsulated aspirin caused insignificant increase of 50% and 75% after the first two instillations but after the third instillation it rose significantly to 150%. After the ascorbic acid-bicorbonate preparation values of <150% were obtained after all three instillations; particularly high levels occurred after the first instillation perhaps due to lower Ph caused by the ascorbic acid. Increased DNA loss occurred after alcohol 10% (strong German beer), 20% (Campari) and 40% (whisky) which was significant after Campari and whisky, the responses being again dose dependent. We conclude that the gastric DNA (cell) loss technique can be used satisfactorily to quantify gastric epithelial damage caused by local chemical insults which in the case of aspirin and alcohol appear to be dose dependent.

T14
Clinical correlates of spiral shaped organisms from antral biopsies

A IRELAND, G HOLDSTOCK, L BOOTH, P HAWTIN, J BAMFORTH, AND A PEARSON *(Southampton General Hospital, Southampton)* There has been considerable controversy recently regarding the findings of spiral like organisms in the stomach and their possible relevance to gastric pathology. To investigate this further, antral biopsies were obtained from 108 unselected patients attending for endoscopy and submitted for histology and culture under microaerophilic conditions. Spiral-shaped gram-negative organisms were cultured in 43 (40%). Patients with positive cultures were more likely to have either a history of ulcer disease (53% *vs* 9% $p<0·0001$) or active ulceration (46% *vs* 9% $p<0·0001$). Only 10 patients of 43 with ulcer disease were negative in culture. Positive culture was also associated with histological evidence of gastritis (88% *vs* 15% $p<0·0001$) and H_2 antagonist use (39% *vs* 15% $p<0·004$), but not with sex, endoscopic evidence of gastritis (19% *vs* 11%) or erosions (7% *vs* 3%). Only 10 of 55 patients with histological gastritis were negative in culture.

Preliminary microbiological studies suggest that these organisms are all similar or closely related strains (Campylobacter-like).

The relevance of these organisms remains obscure, but this comfirmation of their association with ulcer disease and gastritis is interesting and deserves further study.

T15
'Campylobacter pyloridis' in peptic ulcer disease: pathogen or opportunist?

A SMITH, A B PRICE, J DOLBY, AND J LEVI. *(Northwick Park Hospital and CRC, Harrow Middlesex)* 'Campylobacter pyloridis', only recently identified, may have a role in peptic ulcer disease. Therefore a complete microbiological and histological analysis (including scanning electron microscopy) was performed prospectively on 54 sets of endoscopic antral biopsies from 50 patients with varied upper gastrointestinal complaints. The organism was cultured in 16 of the 20 (80%) antral biopsies from patients with an acute duodenal ulcer, four of seven (57%) with a chronic gastric ulcer, five of nine (56%) with a healed gastric or duodenal ulcer, one of two with gastritis only and was absent from two patients with pernicious anaemia. It was present in five of fourteen (36%) 'controls', patients with dyspepsia but normal endoscopy. Significantly these five had abnormal microscopy. Histological correlation was within a classification chronic superficial and chronic atrophic gastritis, active or quiescent. 'C pyloridis' was cultured from 75% with chronic superficial gastritis and 61% with chronic atrophic gastritis. Inflammatory activity (polymorphs infiltrating mucosal

epithelial cells) was of no influence. Organisms were isolated in only one of the 12 (8%) patients with normal antral mucosa. Scanning microscopy identified organisms in two culture negative cases of duodenalulcer raising this group's yield to 90%.

Clearly 'C pyloridis' is strongly associated with peptic ulcer disease, particularly duodenal ulceration. It rarely colonises normal antral mucosa. Whether pathogen or opportunist will partly depend on the careful follow-up of the 36% of colonised 'controls'. Will they develop ulcers?

T16

Campylobacter-like organisms in mucosa of patients undergoing routine upper gastrointestinal endoscopy

J A H FORREST, C R FRICKER, R W A GIRDWOOD, R A BURNETT, AND J B MACDONALD *(Departments of Bacteriology, Pathology and Gastroenterology Unit, Stobhill General Hospital, Glasgow)* Ninety five consecutive patients undergoing routine upper gastrointestinal endoscopy were investigated for the presence of 'campylobacter-like' organisms (CLO) in the stomach and duodenal cap mucosa. Two biopsies were taken from three sites (antrum and body of stomach and duodenal cap) from each patient. One set was examined histologically to determine the degree of gastritis and the presence of CLO; the other set being assessed and micro-biologically by stained smear and culture for CLO.

'Campylobacter-like organisms' were seen in antrum and body of stomach in 56 cases (59%). When present CLO were seen in both antrum and body; this not being so in only two cases. There was an excellent correlation between the demonstration of CLO by histology and culture; disagreement being noted in only five biopsies. Of 70 patients in whom gastritis was diagnosed histologically CLO were detected in the stomach by at least one method in 50 (71%) whereas in the 25 patients with histologically normal stomachs only six (24%) were positive for CLO ($p<0.01$). There was no significant difference between the incidence of CLO in mild (13 of 15 cases) or in severe gastritis (37 of 55) ($p>0.05$). CLO were only seen in duodenal cap mucosa in two cases. Twenty four patients with and two patients without histological evidence of gastritis had endoscopically diagnosed peptic ulceration. Of these 26 patients, 14 had demonstrable CLO (54%).

Although this study has shown that the presence of CLO correlates closely with gastritis we have been unable to demonstrate any positive correlation with peptic ulceration.

T17

Gastric emptying in patients with flatulent dyspepsia, with and without gall bladder disease

P WATSON AND A H G LOVE *(Department of Medicine, The Queen's University of Belfast, Belfast)* A disturbance of antral motility has been implicated in causing symptoms of flatulent dyspepsia associated with gall stones. Antral activity is an important determinant of the rate of gastric emptying of a solid and so it is of note that similar symptoms have been attributed to delayed gastric emptying in a wide range of disorders. The aim of the present study was to determine if gastric emptying is abnormal in patients with dyspepsia, with or without gall bladder disease. Gastric emptying of a scrambled egg meal was measured in 74 subjects for 90 minutes by a fixed scintillation counter method using ^{99}Tc. The subjects were divided into five groups: 24 normal controls in whom gall stones were excluded by ultrasonography; gall stones and flatulent dyspepsia (n=13); gall stones, no dyspepsia (n=12); postcholecystectomy dyspepsia (n=13); radiography/endoscopy negative dyspepsia (n=12). Gastric emptying was significantly slower in the 25 patients with gall bladder disease compared with controls after 45 minutes ($p>0.02$) and for the remainder of the test (p range 0·01–0·03). There was no difference between the two groups with gall bladder disease with or without dyspepsia and both were significantly slower than controls ($p>0.05$). Patients with postcholecystectomy dyspepsia showed delayed emptying after 65 minutes (p range 0·03–0·01). There was no delay compared with controls in patients with radiograph/endoscopy negative dyspepsia. For the three groups with a history of dyspepsia, 22 patients experienced typical symptoms during the test but gastric emptying was not different from controls. It is concluded that gall bladder disease, even after cholecystectomy, is associated with delayed gastric flatulent dyspepsia are not usually associated with delayed emptying.

T18

Antral motor disturbance in functional abdominal pain

S L GRAINGER, JUDITH I GAUNT, D N CROFT AND R P. H THOMPSON *(Gastrointestinal Laboratory, Rayne Institute, St Thomas' Hospital, London)* The irritable bowel syndrome accounts for up to 50% of referrals to gastroenterological clinics. In one-fifth abdominal pain occurs without altered bowel habit and conventional investigations are normal. Associated symptoms in these patients often suggest disturbed gastric motility and we have previously observed delayed initial gastric emptying of a solid in such patients.

Twenty three patients with functional abdominal pain and normal bowel habit, and with normal upper GI endoscopy and gall bladder ultrasound were studied. After an overnight fast, gastric emptying of 99m Tc-labelled poached egg white was measured with a gamma camera/computer system. Gastric emptying measurements were repeated 30 minutes after one month's double blind treatment with either metoclorramide 10 mg tds (n=8), domperidone 20 mg tds (n=8) or placebo (n=7).

Pre-treatment gastric emptying confirmed the prolonged lag time before the start of emptying. Neither domperidone nor placebo had any influence on the lag time or gastric emptying rate. Metoclopramide, however, shortened the lag time (before 22·5 min, after 14·5 min, SE of difference 2·6, $p=0.016$) and normalised the pattern of gastric emptying.

Domperidone is a dopamine antagonist, but metoclopramide is also cholinomimetic. The former inhibits adaptive relaxation of the gastric fundus, the latter also enhances antral motor activity. The differential effect of the drugs on gastric emptying in our patients suggests the prolonged lag time is due to a defect of cholinergic activity or of contractility in the antral 'pump'.

T19

Stress-induced suppression of antral motility in functional dyspepsia

M CAMILLERI, J R MALAGELADA (INTRODUCED BY S F PHILLIPS) *(Gastroenterology Unit, Mayo Clinic, Rochester, Minnesota, USA)* In healthy individuals, acute stress inhibits the antral pressure response to a meal, and delays its emptying from the stomach. It is not known whether patients with functional dyspepsia (FD) respond to stress in a similar manner. We studied 12 patients (age range 20-51, mean 35·8; five men, seven women) afflicted with nausea, vomiting, epigastric discomfort or bloating by means of a pneumohydraulic multilumen

perfusion system, with or without stressful stimulation to the hand by a transcutaneous electrical nerve stimulator (TENS). The control group was composed of 12 healthy volunteers, six of whom underwent the study with active TENS, and six with sham TENS. Transcutaneous electrical nerve stimulator was applied for one hour starting 10 minutes after the end of the solid-liquid meal, at an intensity that was just bearable in each individual. Sequential 20 minute antral motility indices (MI = $\log_e$ [sum of amplitude × number of waves + 1]) were calculated from the antral phasic pressure activity in each study, and the slopes of cumulative 20 minute MI before and during one hour TENS were determined.

Without TENS, seven FD patients (group I) had normal antral motility (0·554 ±0·009 *vs* controls with sham TENS 0·574 ±0·005) and five (group II) had decreased motility (0·477±0·011, all slopes being below 5th percentile for controls: range 0·543-0·597). With TENS, antral motility was suppressed in group I (0·518±0·009, $p<0·05$) but remained unchanged in group II (0·502±0·005). The degree of suppression of antral MI slopes during TENS was similar in group I patients and healthy individuals.

We recognise two groups of patients with FD: (I) those with normal postcibal antral motility which is normally inhibited by acute stress; and (II) those with decreased motility unaffected by stress. Such a distinction may reflect differences in the gastric response to stress or its perception, and may influence the choice of therapy.

T20

Effect of gall bladder function on duodenogastric reflux

W G CHEADLE, V PATHI, C R MACKIE, AND A CUSCHIERI *(University Department of Surgery, Ninewells Hospital and Medical School, Dundee, Scotland)* Symptomatic enterogastric reflux after gastrectomy is well recognised, but controversy exists about primary duodenogastric reflux as a clinical entity. The occurrence of previous cholecystectomy has been frequent in those patients with epigastric symptoms and endoscopic bile gastritis, and cholecystectomy has been incriminated as a causitive factor of bile reflux. Seventy two patients, of whom 55 had cholelithiasis and 17 had undergone a previous cholecystectomy, and 43 asymptomatic volunteers were studied for the presence of duodenogastric reflux using intravenous 99m Tc-HIDA with milk provocation. Seventeen of the 55 patients with cholelithiasis have been studied prospectively after cholecystectomy as well. The subjects were scanned in the erect position and control films obtained after injection of the HIDA. They were then scanned for one hour after ingesting 300 ml milk, and counts in the gastric field were expressed as a percentage of the total at five minute intervals. The gall bladder was assessed during the test and identified as functioning, poorly functioning, or non-functioning depending on the degree of count density in the gall bladder field and its emptying curve in response to milk by on-line computer analysis. Results were compared by both the χ^2 and Mann-Whitney U-tests. Reflux was shown in eight of the 43 volunteers, but was greater than 3% in only three which constituted a positive test. In the cholelithiasis group, the gall bladder function was normal in 34, impaired in 11, and absent in 20. In those without function there was a significantly higher incidence ($p<0·05$) and amount ($p<0·01$) of duodenogastric reflux. In all patients who underwent cholecystectomy (n=34), there was also significantly more reflux ($p<0·001$) than that seen in the volunteers. In the 17 patients studied prospectively, 12 had no reflux before or after, two had reflux before which did not change after cholecystectomy, and three developed reflux after cholecystectomy.

These results indicate that patients with cholelithiasis and a non-functioning gall bladder or those who have undergone cholecystectomy are more prone to deuodenogastric bile reflux.

T21

How effective is the 50 cm Roux in preventing reflux of bile acids into the gastric remnant: a 24 hour study?

V POXON, B HOGG, AND M R B KEIGHLEY *(Department of Surgery, General Hospital Birmingham)* It has always been assumed from isotope scans and measurement of bile acid concentrations in gastric juice that a long Roux Y loop prevents bile reflux.

We have collected gastric juice by hourly aspiration over 24 hours from six healthy subjects two years after Roux Y bile diversion when a loop of at least 50 cm in length was used. Aspirates were analysed for pH, bacterial counts and bile acid concentrations. The pH was invariably greater than 4·0 and there was persistent bacterial overgrowth with between 10-18 different species in each patient. Peak hourly bile acid concentrations greater than 5·0 umol/l were recorded in only one patient but there were two others with peak hourly bile acid concentrations greater than 0·5 umol/l. There was marked fluctuation in bile acid concentrations over the 24 hours of the study and reflux would not have been identified from a standard fasting two hour aspirate in two of the three patients with high bile acid concentrations. These results indicate that bile reflux may occur despite a 50 cm Roux and was excessive in at least one of the six subjects studied.

T22

Acid perfusion of duodenal ulcer craters and ulcer pain – a controlled double blind study

J Y KANG, AND IVY YAP *(Medical Unit II, National University of Singapore, Singapore General Hospital, Outram Road, Singapore)* Early uncontrolled observations showed a close relationship between peptic ulcer pain and intragastric acidity. More equivocal results were, however, reported by subsequent workers and a recent controlled study of gastroduodenal acidification and ulcer pain suggested that 'duodenal ulcer pain is largely and possibly totally unrelated to duodenal acidification'.

Patients who satisfied the following criteria were included in the present study: (1) Each patient must have a history of upper abdominal pains related to food and relieved by antacids. (2) The last episode of pain must have occurred within 24 hours of the time of study. (3) An active duodenal ulcer must be demonstrable at endoscopy.

Nineteen patients were studied. There were 18 men and one woman and their ages ranged from 19 to 71 years. Informed consent was given. Endoscopy was performed under local anaesthesia using the Olympus GIFQ or Q10 gastroscope. No premedication or sedation was given. Using a washing tube 100 ml normal saline and 100 ml 0.1N hydrochloric acid were infused sequentially onto the duodenal ulcer crater over five minute periods. The order of infusion was randomised and double blind. If the patient reported pain on one solution infusion of that solution was terminated.

Eight out of 19 patients reported pain when acid was being perfused. One patient reported pain when saline was being given ($p<0·025$). Seven out of the eight patients developing pain on acid reported that the pain was similar to their usual ulcer pains. If the patient with atypical pain was excluded the difference between acid and saline remained significant ($p<0·05$). In six

patients who developed pain on acid the infusate was changed to saline until the pain has subsided. Acid was then reinfused. In five instances the pain was reproduced.

Acid therefore appears to have a role in the production of duodenal ulcer pain although other factors are likely to be important also.

T23

Duodenal loop alkalinisation in DU: stimulus or response?

J M RAWLINGS, B J Z DANESH, D FARAH, A N H MAIN, R J MORGAN, W MURRAY, M L LUCAS, AND R I RUSSELL *(Institute of Physiology, Glasgow University, Gastroenterology Department, The Royal Infirmary, The Department of Surgery, The Western Infirmary, Glasgow)* Mucosal and intraluminal pH measurements have been made in the stomach and duodenum of 64 patients undergoing upper gastrointestinal endoscopy, with or without anti-cholinergic premedication. A catheter pH electrode inserted down the biopsy channel allowed *in situ* pH readings at standardised sites. Patients were divided into two groups, those with no endoscopic abnormality (n=43, 17 from an ERCP study); those with duodenitis or an active duodenal ulcer (n=21).

Without anticholinergic premedication, control patients had an acid gastric fundal lumen and a neutral duodenal loop mucosal surface, pH of 7·02±0·12(7); 6·87±0·10(17) at ERCP. Patients with duodenitis or active DU also had acid gastric fundus lumen values with a strikingly alkaline duodenal surface of pH 7·74±0·04(7).

When anti-cholinergic premedication was used, luminal pH in the fundus was reduced in both groups as expected but the DU group fundal pH remained lower than normal. Duodenal mucosal surface pH did not change in the controls but there was a highly significant reduction ($p<0·001$) in the DU group to 6·99±0·17(14).

Two notable features therefore occur in the DU group. Firstly, lower than normal gastric fundal pH persists, despite cholinergic and H-2 receptor blockade: secondly, duodenal alkaline secretion, as mucosal surface pH is significantly above assumed plasma values. This is predicted by the cytoprotection hypothesis and may be a response to increased duodenal acid loads in DU. Loop pH fell, however, while fundal pH rose after atropinisation, while normal loop pH did not change. An alternative hypothesis is that high duodenal pH in DU is itself pathological and causes inappropriately high acid secretion as a consequence.

T24

Comparison of tripotassium dicitrato bismuthate (TDB) tablets and cimetidine in the healing and long term relapse of duodenal ulcer.

I HAMILTON, H J O'CONNOR, N C WOOD, AND A T R AXON *(Gastroenterology Unit, General Infirmary at Leeds, Leeds)* In a double blind endoscopically controlled trial, TDB tablets (1 qds) were compared with cimetidine (1 g daily) in the treatment of duodenal ulcer (DU). Eighty patients (58 men, 22 women, mean age 45 years, range 22-72 years) with DU were randomly allocated to treatment with either TDB (41 patients) or cimetidine (39 patients) for six weeks. Patients kept a daily record of symptoms on a diary card and ulcer healing was determined by endoscopy during the final week of treatment. In those who had healed, a further endoscopy was done at one year, or earlier if symptoms recurred. The groups were similar with respect to age, sex, smoking and duration of ulcer symptoms. Healing occurred in 33 (80%) treated with TDB and 29 (74%) treated with cimetidine (χ^2, $p>0·05$). Relief of symptoms was similar with both drugs. No significant difference was seen in the early relapse rate (up to nine months follow up) after healing with either drug. Late relapse (>9 months follow up) was significantly more common in patients whose ulcers had initially been healed with cimetidine. At 16 months, 13 of 30 (43%) given TDB, compared with 18 of 23 (78%) given cimetidine, had relapsed (χ^2, $p<0·02$). Eighty seven per cent of relapses were symptomatic. Our results suggest that TDB tablets are as effective as cimetidine in the short-term treatment of DU and, moreover, appear to be superior in the long term prevention of ulcer recurrence.

T25

Are pirenzepine and cimetidine additive or synergistic in combination?

M DEAKIN, J K RAMAGE AND J G WILLIAMS *(RN Hospital, Haslar, Gosport, Hampshire, UK)* The effect of cimetidine (C) and pirenzepine (P) has been shown to be greater in combination than when the individual drugs are given alone, but it is not clear whether this is a simple additive or a synergistic effect. We have monitored 24 hour intra-gastric pH in eight asymptomatic volunteers with a past history of duodenal ulceration. Each subject received placebo, C 400 mg bd, P 50 mg bd, C 400 mg with P 50 mg bd, or C 200 mg with P 25 mg bd on five separate occasions. The data were analysed as hydrogen ion activity using Wilcoxon's rank sum test.

Mean hourly hydrogen ion activity during the total 24 hours was significantly lower with the lower dose combination (6·45±1·5 SEM) than with P (16·9±4·1, $p<0·05$) or C (11·9±2·8, $p<0·05$) alone. The higher dose combination produced similar inhibition (7·09±1·5) but this did not reach statistical significance. At night both combination treatments (high dose 1·75±0·7, low dose 2·91±1·1) were significantly better than P (13·9±4·5, $p<0·05$) but not better than C (3·5±0·09) alone.

We conclude that a low dose combination of C 200 mg and P 25 mg is significantly better in inhibiting intragastric acidity over a 24 hour period than either drug given alone at twice the dosage: this is suggestive of a synergistic effect between the drugs in combination.

T26

Intravenous omeprazole rapidly raises intragastric pH

R P WALT, J R REYNOLDS, M J S LANGMAN, H L SMART, K W SOMERVILLE, G KITCHINGMAN, AND C J HAWKEY *(Departments Therapeutics and Surgery, University Hospital, Nottingham)* Intravenous antisecretory drugs are often used to treat upper GI bleeding and to prevent stress ulceration. Their effects on 24h intragastric acidity, however, have been poorly studied. Omeprazole, an H^+K^+ ATPase inhibitor, is the most potent oral antisecretory agent used in man. We have studied the effect on 24h intragastric acidity of intravenous omeprazole in five duodenal ulcer patients. Two dosage regimens (80 mg at 0900h with 40 mg at 1700h [A], and 80 mg at 0900h with 80 mg at 1700h [B]) were compared double blind with placebo given at the same times in random order. In a fourth study three patients received three doses of omeprazole (80 mg at 0900h, 40 mg at 1700h and 40 mg at 0100h [C]). The drugs or placebo were infused over 12 minutes by mechanical pump. Acidity was measured on hourly aspirates of gastric contents with a glass electrode. Meals were identical in all studies. Mean (± SEM) intragastric acidity (1000-0800h) fell from 34·3±4·3 mmol/l on placebo to 2·1±0·9 mmol/l [A], (− 94% $p<0·001$ anov) and to

0·7±0·2 mmol/l [B], (− 98%). The intragastric pH remained <4·0 for 95% of recordings on placebo and for 20% of recordings after either [A] or [B]. pH values were <4·0 for only 10% of recordings and mean intragastric acidity decreased by 99% to 0·5±0·4 mmol/l with regimen [C]. Gastric pH rose to >4·0 in all patients one hour after the first infusion of omeprazole. Ph remained at about this level for the majority of the next 23 hours. Unexpectedly large doses of intravenous omeprazole were needed to achieve this compared with earlier studies using oral omeprazole. Intravenous omeprazole may be of use when rapid and prolonged neutralisation of gastric acid is required.

PANCREATICOBILIARY
T27–40

T27
Effect of Ceruletide on the human choledochal sphincter in patients undergoing cholecystectomy

A CUSCHIERI, J G R CUMMING, R A B WOOD, AND P R BAKER *(University Department of Surgery, Ninewells Hospital & Medical School, Dundee, Scotland)* The effect of the synthetic peptide Ceruletide on the human choledochal sphincter complex has been investigated in 20 consecutive patients undergoing cholecystectomy either for previous acute cholecystitis/biliary colic (group I, n=14) or gall stone associated pancreatitis group II (n=6) using a standardised technique of pump driven isotonic saline perfusion manometry. Each patient had two pressure profile studies with Ceruletide (1·0 μg iv) being administered before the second run. All patients included in this study had a normal intra-operative cholangiogram. Statistical analysis was by a non-parametric test for paired and unpaired data (Wilcoxon's signed-ranks and Mann-Whitney U tests). There was no difference in the basal pressure between the two groups. The postinfusion pressure in group I ($\bar{x}$10·0± 1·03 mmHg) was significantly higher than the basal pressure ($\bar{x}$6·57±0·68 p<0·02). The postinfusion pressure in group II $\bar{x}$ 7·5 ± 2·26 as opposed to a basal pressure of 6·66 ± 2·16 (NS).

Before injection of Ceruletide a significant residual pressure (postinfusion minus basal >2mmHg) was encountered in 7/14 in the cholecystitis/biliary colic group. The residual pressure was abolished by Ceruletide in all these cases. The mean residual pressure in the cholecystitis/biliary colic group was 3·57±0·78 mmHg compared with 0·83±0·40 in the pancreatitis group (p<0·05). Ceruletide did not lower the postinfusion or residual pressure in the pancreatitis group.

This study has shown that Ceruletide has a marked relaxant effect on the human choledochal sphincter. Previous pancreatitis is associated with an atonic, functionally unreponsive sphincter.

T28
Patency of the biliary sphincter after transduodenal sphincterotomy. A review of 25 years surgical experience

A R W HATFIELD, C PANAHY, AND H D RITCHIE *(Academic Department of Gastroenterology and Surgical Unit, The London Hospital, Whitechapel, London)* Of 191 patients who underwent transduodenal sphincterotomy and exploration of the bile duct at The London Hospital between three and 24 years ago (mean 9·5), 34 volunteered for re-examination by ERCP. In nine patients (26%) the sphincterotomy site was wide open and in 25 (74%) it had partially or completely returned to a normal appearance. Of these 25 patients, 14 had a small slit like orifice on the papilla, seven had a completely normal looking papilla and in four there was a small hole above an intact papilla. Healing of the sphincterotomy did not correate with the period of time after surgery. In no patient were gall stones demonstrated.

A balloon catheter was used to assess sphincterotomy size and the pressure gradient from bile duct to duodenum measured with a side hole perfused catheter. The nine gaping orifices usually took a 10 mm balloon and had little or no pressure gradient (mean–1·5 cm H_2O). Although those with slit like orifices and normal papillae usually took a 5 mm balloon and had higher pressure gradients (mean–30cm H_2O), there were four patients with endoscopically intact papillae through which a 5 mm balloon could not be pulled and pressure gradients that did not change after TT glucagon. These four patients probably had some degree of sphincterotomy stenosis. They were all, however, asymptomatic.

Bile was aspirated from the bile duct for culture in 32 patients and found to be positive in 17 and negative in 15. Although none of the patients had clinical cholangitis, of those with air-reflux into the biliary tree, nine of 16 had infected bile compared with two of 15 without air in the billiary tree.

There is a tendency for surgical sphincterotomies to heal with time back to a near normal state and providing that gall stones have been completely removed, this may not be disadvantageous.

T29
Long term patency of sphincteroplasty: a radiolological review

C F HARVEY, C J H LOGAND, AND K WILSON, (INTRODUCED BY T G PARKS) *(The Ulster Hospital, Dundonald, Belfast.)* Sphincteroplasty, first described by Jones (1952) in combination with transduodenal exploration of the common bile duct may offer certain advantages. Jones (1973) emphasised that sphincteroplasty is only considered adequate when the complete sphincter is divided surgically and that the demonstration of free biliary reflux on barium meal is essential to show continued patency of the sphincteroplasty. Continued patency should prevent ascending cholangitis and allow the passage of retained stones.

Over a five year period 27 patients underwent sphincteroplasty. The mean age was 60 years and M:F ratio was 11:16. Fourteen patients were jaundiced at the time of surgery and the mean pre-operative bilirubin in these patients was 176 mm/1.

In 20 patients reviewed there were no clinical episodes of jaundice or cholangitis and liver function tests were normal. Barium meal examination was performed in 14 patients at a mean follow-up time of 32 months (range 11-68 months).

Patency of the sphincteroplasty as shown by entero-biliary reflux was present in seven cases and asymptomatic retained stones were demonstrated in one of these.

It appears that many sphincteroplasties may not remain adequate as defined by the demonstation of free biliary reflux and even where free reflux is demonstrated residual calculi may be present.

T30
Prospective randomised trial of early versus delayed surgery for actute biliary tract disease.

B W A WILLIAMSON, C J SIMPSON, G McLATCHIE, G GILLESPIE, AND C S McARDLE *(Departments of Surgery, Royal and Victoria Infirmaries and Southern General Hospital, Glasgow)* Prospective randomised studies from specialised centres in Scandinavia and the UK have shown that early surgery in

acute cholecystitis is not associated with increased morbidity and mortality. The value of this policy in routine surgical practice has not been assessed.

Fifty patients with proven acute biliary tract disease presenting to three hospitals were randomised to early (n=26) or delayed (n=24) surgery. Groups were similar with respect to age, sex, mode of presentation and clinical findings.

There was one postoperative death from pulmonary embolism in the early group and one from postoperative sepsis in the delayed group. Five patients allocated to delayed surgery failed to settle on conservative management and require emergency cholecystectomy. A further three patients, died, two of gall bladder sepsis, before readmission for surgery. Postoperative morbidity in the 16 patients undergoing delayed surgery were similar to that in the early group; overall hospital stay was longer. All but one death occurred in patients older that 80 years.

These results emphasise the aggressive nature of acute biliary tract disease particularly in the elderly and confirm the value of early surgery.

T31

Prospective study of the use of a pocket computer in the prediction of common bile duct stones

C P ARMSTRONG, T V TAYLOR, S LUCAS, AND J JEACOCKS *(Departments of Surgical Gastroenterology and Computation, Manchester Royal Infirmary, Oxford Road, Manchester)* Many surgeons do not routinely use operative cholangiography at the time of cholecystectomy. An alternative method for predicting the presence of common bile duct stones using a pocket computer has been prospectively evaluated. Thirty six variables were assessed on each of a consecutive series of 424 patients undergoing cholecystectomy and used as a data base. Using multivariate analysis, six variables were selected to predict the presence of bile duct stones; bile duct diameter, patient's sex, history of jaundice, or pancreatitis, a presentation of biliary colic and the number of stones in the gall bladder.

A prospective study was then carried out of a second group of 242 patients also undergoing cholecystectomy. Using the initial data base 93% of this prospective group were correctly classified, when compared with the corresponding operative cholangiography. Bile duct stones were predicted in 17 (7% false positive) patients in whom they did not exist and stones were overlooked in only one patient (0·4% false negative). Thus the pocket computer had a sensitivity of 99·6% and a specificity of 93% in the detection of choledocholithiasis.

Using this system of multivariate analysis and using a pocket 'mini-computer' (Sharp) very few bile duct stones will be overlooked and the incidence of negative exploration of the common bile duct will be low. We believe that this technique is a useful method for the operative determination of choledocholithiasis.

T32

ABSTRACT WITHDRAWN

T33

Quantification of biliary excretion and gall bladder bile concentration of temocillin in man

D P MAUDGAL, A LANZINI, AND T C NORTHFIELD *(Departments of Medicine, St. George's Hospital Medical School, London)* Pharmacokinetics is concerned with measuring serum and urinary concentrations of drugs, while biliary excretion is a neglected area. We have therefore applied techniques developed for measurement of biliary lipid secretion and biliary lipid mass in the gall bladder (GB) to biliary excretion of an antibiotic (Temocillin – a new synthetic, long-acting parenteral ß-lactum said to be of particular value in biliary tract infections). We have carried out eight studies in six subjects with normal hepatobiliary and renal function. In each study, duodenal perfusion was carried out with polyethylene glycol, and IV injection of Temocillin (0.5 g in three and 1 g in five studies) was given after a 60 minute equilibration period. ^{99m}Tc HIDA (1mci) was given iv as a GB bile marker. Serum, intestinal aspirate and urine were collected over six hours, and then a GB ultrasound was carried out to determine GB volume and a scintiscan to could ^{99m}Tc HIDA activity over the GB. Gall bladder bile was collected for Temocillin and Tc HIDA activity following cholecystokinin infusion. Plasma half life was 210 minutes at both doses and mean urinary excretion accounted for 35% and 38% respectively. Mean biliary excretion of Temocilin was 2.2% of the administered dose, and mean hepatic bile concentrations was 10 ug/ml, while GB bile concentration was 474 ug/ml. We conclude that biliary drug excretion can be studed quantitatively; and that this route of excretion accounts for only a small proportion of administered Temocillin, but that this drug is highly concentrated in the normal GB.

T34

Measurement of biliary lipid mass within the gall bladder in health and in ileal Crohn's disease

R P JAZRAWI, C BROWN, AND T C NORTHFIELD *(Department of Medicine, St. George's Hospital Medical School, London)* Identification of supersaturated gall bladder bile gives no indication of whether the underlying cause is a deficit of bile acid and/or phospholipid or an excess of cholestrol. In order to make this distinction, we have developed a method of measuring biliary lipid mass within the gall bladder following iv injection of ^{99m}Tc HIDA. Activity over the gall bladder is measured by camera, and a sample of gall bladder bile then obtained for isotopic and chemical determination, and biliary lipid mass is derived from the following formula:

$$\frac{\text{mass in sample}}{\text{TcHIDA in sample}} = \frac{\text{mass in GB}}{\text{TcHIDA in GB}}$$

We have applied this technique to nine patients with ileal Crohn's disease and to 12 healthy controls. In three patients we have validated this indirect measurement by comparing it with direct measurement of mass for all three biliary lipids after surgical removal of the gall bladder (r= 0·99, p=0·0001). The ileal Crohn's group had a significantly higher saturation index, and this was because of a reduction in bile acid and phospholipid mass (mM) without any

Group	n	SI	BA	PL	XOL
Ileal Crohn's	9	1·36±0·11	2·4±0·5	0·8±0·2	0·31±0·06
Healthy controls	12	0·93±·07	4·9±0·3	1·6±0·3	0·47±0·09
		<0·005	<0·005	=0·05	NS

significant alteration in cholestrol mass.

We conclude that our method of measuring biliary lipid mass is valid, and that it provides a rapid new method of determining the underlying cause of supersaturated gall bladder bile.

T35

Intestinal transit rate, deoxycholic acid and the cholesterol saturation of bile

S N MARCUS AND K W HEATON *(University Department of Medicine, Bristol Royal Infirmary, Bristol)* There is considerable

evidence that the level of deoxycholic acid (DCA) in the bile influences biliary cholesterol saturation. Deoxycholic acid is formed in the colon and absorbed slowly. Hence, changes in colonic transit rate might influence biliary DCA and the cholesterol saturation of bile.

When 10 constipated subjects took standardised senna tablets for six weeks in a dose sufficient to reduce mean whole gut transit time from 137 to 48h, DCA as a proportion of biliary bile acids fell from 24.6±3.2 to 15.6±6.9% (p=0·004) and DCA pool measured by isotope dilution fell from 0·61±0·13 to 0·41±0.11g (p=0·006). In those subjects (n=5) whose bile was initially supersaturated with cholesterol and whose transit time fell by >24h, the saturation index fell from 1·5±0·1 to 1·2±0·1 (p=0·03).

Conversely, when eight normal volunteers took loperamide capsules sufficient to prolong mean transit time from 48 to 113h, the DCA pool increased from 0·37±0·09 to 0·54±0·08g (p=0·001). Mean biliary DCA increased to a lesser extent, from 17·1 to 20·9% (p=0·065), because the estimated total bile acid pool expanded (from 2·10± 0·17 to 2·64±0·25g; p=0·04), presumably due to loperamide slowing down small bowel transit. Despite this expansion of the bile acid pool, loperamide increased the cholesterol saturation index from 1·1±0·1 to 1·3±0·1 (p=0·02).

Thus, manipulating colonic transit rate alters the size of the DCA pool and bile cholesterol saturation. These findings suggest that slow colonic transit might increase the risk of supersaturated bile and hence of gall stones.

T36

Cholehepatic shunt pathway: new concept in hepatic transport

K R PALMER, A F HOFFMANN, E B LJUNGWE, AND D GURANTZ *(University of California, San Diego, CA, USA)* Bile acid dependent flow (BADF) is attributed to the osmotic properties of secreted BA. Using the unnatural C-23 BA nor-chenodeoxycholate (nCDC) as a probe, we examined the hypothesis that BADF is influenced by ductular events.

C^{14}-nCDC was intravenously infused into hamsters and rats with biliary fistulae. In hamsters biliary recovery of C^{14}-nCDC was incomplete. The nuclear moiety of the BA was partially oxidised and hydroxylated. Forty one per cent was secreted in unconjugated form while the remainder was conjugated with taurine. n-CDC induced an enormous canalicular choleresis of 231 ul/umol secreted BA ; nCDC–taurine (9·5) and chenodeocycholate (21) were much less choleretic.

In the taurine replete rat, nCDC was principally secreted as nCDC-taurine and was moderately choleretic (18); taurine depletion decreased BA output, and choleresis was greatly enhanced (55). In both animals nCDC increased bicarbonate output.

We suggest that the intrinsic choleretic effect of nCDC ions is amplified by passive ductular reabsorption of the protonated unconjugated BA which is then returned to the hepatocyte by the peribiliary plexus and resecreted into the canaliculus. The proton is derived from carbonic acid, so that BA anions are replaced by bicarbonate ions. Conjugated nCDC is less choleretic because its strong acid group prevents ductular reabsorption.

This cholehepatic shunt pathway may explain the greater choleretic effect of unconjugated BA compared with their conjugates, may also explain the choleretic properties of many weak acids, and provides insight into the functional importance of BA conjugation.

T37

Induction of cytochrome P450: unifying factor in pancreatic disease

D W K ACHESON, P N SHAW, J B HOUSTON, AND J M BRAGANZA *(University Department of Gastroenterology, Manchester Royal Infirmary and Pharmacy Department, Manchester University)* The hepatic cytochrome P450 complex metabolises a wide range of substrates – both endogenous and exogenous – and is 'induced' by many of the lipophilic drugs and xenobiotics that it processes. Biotransformation usually results in detoxification but, on occasion, highly reactive metabolites are generated which can cause hepatic necrosis and derange the secretory pathways of exportable proteins.

Pharmacokinetic studies using antipyrine and theophylline assess overall cytochrome P450 and cytochrome P448 activity respectively, and we have applied these methods to 35 consecutive patients with acute pancreatitis, chronic pancreatitis or pancreatic cancer. The drugs were given orally on separate days, under standardised conditions, and their concentrations in serial blood samples were measured by HPLC. There was good correlation between the half life (T½) and clearance (CL) of each compound and between each parameter for the two drugs. The CL of each drug was significantly faster in patients with all forms of pancreatic disease compared with controls.

Alcohol was the obvious inducer in 10 patients (27%): in the remainder dietary, social, occupational, domestic or iatrogenic exposure to xenobiotics may be the cause of both the induction of cytochrome P450, and of pancreatic disease. It is conceivable that the pancreas has a latent cytochrome P450 complex – as does the intestine, kidney and lung – and that pancreatic disease is a consequence of local detoxification reactions. Alternatively the abnormal bile in our patients may be the link between hepatic induction and pancreatic disease.

T38

Accuracy of pre-operative arteriography in the assessment of resectability in pancreatic carcinoma

A R W HATFIELD, JANET B MURFITT, R W MOTSON, A D W MACLEAN, AND J E LENNARD-JONES. *(Academic Department of Gastroenterology, Department of Radiology and Department of Surgery, The London Hospital, Whitechapel, London)* Few pancreatic carcinomas are found to be suitable for radical resection at laparotomy. With the advent of the non-operative management of malignant obstructive jaundice with endoprosthesis insertion, however, it is important not to deny the younger, fit patient the chance of resection, should this be possible.

This present study assessed the accuracy of arteriography, over the last two years, in determining resectability in 17 consecutive patients with pancreatic carcinoma, demonstrated by ERCP and without liver secondaries on ultrasound scanning, in whom the age and general condition would permit an attempt at radical resection.

Coeliac and superior mesenteric arteriography with delayed views of the portal venous circulation were performed preoperatively in all 17 patients. Involvement of the superior mesenteric artery or vein or of the portal vein were considered to imply that the tumour would not be technically resectable.

In 10 patients the arteriogram showed no signs of major arterial or venous involvement but at laparotomy only five were resectable and in five the tumour was involving the superior mesenteric and/or portal vein, thus precluding resection. In seven patients the arteriogram showed non-resectability and this was confirmed at

laparotomy in all seven.

A normal arteriogram does not imply that a tumour is resectable but an abnormal arteriogram appears to accurately predict non-resectability. Patients with tumours judged non-resectable on arteriographic evidence can therefore be managed, if jaundiced, by a non-operative endoprosthesis technique without the fear of denying a younger patient the chance of surgery and a radical resection.

T39

Bacteraemia in the closed duodenal loop bile infusion model of acute pancreatitis

I A GOULBOURNE AND G C DAVIES (INTRODUCED BY R C HEADING) *(University Department of Clinical Surgery, Royal Infirmary, Edinburgh)* The animal model described by Chetty consistently produces haemorrhagic pancreatitis. Distension of the loop with infected bile might produce bacteraemia which could account for pulmonary abnormalities previously described. We have studied this model, using specific pathogen free rats. Two groups (n=46 and 4) had pancreatitis. A third group (n=44) had infected bile injected into a closed small bowel loop (intestinal continuity maintained with a plastic tube). A fourth group (sham gastrotomy) acted as controls. Animals were killed at six hours, except group 1 (18 h) Pancreatitis was confirmed by raised amylase concentrations in groups 1 and 2. Heart and inferior vena caval blood from groups 1, 2 and 3 grew mixed aerobic and anaerobic organisms. Group 4 cultures were sterile. Lungs were inflation preserved for scanning electron microscopy (SEM). Scanning electron microcopy sections at 300x and 1000x from group 3 were identical to controls. Pancreatitis caused marked derangement of lung architecture with incompletely expanded alveoli, which had oedematous distorted walls. Lining cells were disrupted, cracked and covered in debris. The Chetty model of pancreatitis produces bacteraemia. Pancreatitis is necessary for lung abnormalities to develop, however, as animals bacteraemic from a small bowel loop preparation are free from SEM abnormalities.

T40

Born again spleen – but is there life after death?

S NICHOLSON, G H HUTCHINSON, T HAWKINS, B PAUL, AND C W VENABLES *(Departments of Surgery, Medical Physics and Haemotology, Freeman Hospital, Newcastle upon Tyne)* Overwhelming infection, the most feared post splenectomy complication has been prevented in animal studies by splenic autotransplants.

A study was undertaken to determine whether, after removal of the normal spleen, it was possible to preserve splenic function by seeding autoplastic splenic fragments into the peritoneal cavity.

Five patients (aged 24–59 years) required splenectomy for access during distal pancreatectomy for chronic pancreatitis. At the end of the procedure approximately 30–50g of the spleen was diced and the fragments wrapped in a pocket of greater omentum.

The survival and function of the splenic tissue was assessed 5–23 months post implantation. Although postsplenectomy RBC morphology persisted, in no patient was thrombocytosis observed, and splenic phagocytic function was demonstrated in three of the five patients using $^{99}Tc^{m}$–labelled heat-damaged autoplastic erythrocyte scintigraphy. In one patient a second laparotomy provided a neo-splenunculus for histological examination.

This pilot study has shown that this simple technique merits consideration whenever a normal spleen is removed.

INFLAMMATORY BOWEL DISEASE
T41-54

T41

Controlled comparison of enemas containing 1g and 2g 5 aminosalicylic acid in patients with ulcerative proctosigmoiditis.

J POWELL-TUCK AND R A PARKINS *(Department of Gastroenterology, Charing Cross Hospital, London)* We report a double blind trial of enemas containing 1g and 26 5 amino-salicylic acid (5ASA) in 25 patients with ulcerative colitis diagnosed clinically, sigmoidoscopically, and histologically and shown on barium enema to be confined to the rectosigmoid. Patients were included if they had active disease and were taking no medication for its treatment except sulphazalazine (SASP) which was continued in unaltered dose. The trial lasted 28 days with assessment at entry and days 14 and 28 by clinical grading of malaise, bowel frequency, stool consistency, rectal bleeding, sigmoidoscopy and rectal biopsy and possible side effects. Twelve patients (six taking SASP) were randomised to receive each night one 1g enema and 13 patients (three taking SASP) to receive 2g. Among the patients receiving 1g enemas, three were in remission at day 14 and eight at day 28 (non-friable mucosa at sigmoidoscopy, no malaise, two bowel actions or less in previous 24 hours, no rectal bleeding, normal stool consistency) while among those receiving 2g enemas, two were in remission at day 14 and four at day 28. Separate assessment by clinical sigmoidoscopy and histological grades showed no trend toward an advantage for 2g enemas. The combined response rate (overall improvement by day 28) was 62%. Our study shows no sign that 2g enemas are superior to 1g enemas and because 1g enemas are pharmaceutically simpler to keep stable and 2g enemas rather more prone to cause side effects we suggest that 1g is the dose of choice in active distal colitis.

T42

Place of the gastrointestinal surgeon in an infectious disease hospital

R M SMITH, J STEWART AND T G BRENNAN (INTRODUCED BY PROF. G R GILES) *(Seacroft Hospital, Leeds)* Between 1977 and 1983, 15 000 patients presented to a sub-regional infectious diseases unit, of these 186 (1·25%) did not have a specific infectious disease but were shown to have an underlying condition needing surgery, often as an emergency. On the basis of the presenting symptoms and signs three diagnostic groups were identified.

Group 1: gastroenteristis, 142 patients, 19 infants had pyloric stenosis and 11 an intussusception, 11 children had appendicitis and 38 adults had inflammatory bowel disease, 12 colonic neoplasia and others a wide variety of other problems. The children with appendicitis all had complictions at surgery and 65% of the adults with colitis required urgent colectomy despite the use of an intensive steroid regimen after diagnosis. In four patients with inflammatory bowel disease and three with colonic neoplasia the diagnosis was obscured and delayed by the positive culture of a common infecting organisum. 30 patients annually with a specific gastroenteritis also develop the signs of peritonitis, these patients tend to settle and laparotomy can often be avoided.

Group 2: infectious hepatitis, 33 patients: the jaundice was due to pancreatic carcinoma in 63% and choledocholithiasis in 33%. Six patients had 2° hepatic carcinoma.

Group 3: pyrexia of unknown origin, 11

patients: this group included cases of occult abdominal absesses, cholangitis, chronic pancreatitis and gonnococcal peritonitis.

We conclude that patients thought to have an infectious disease often have surgical problems and that specific gastroenteritis may mimick the surgical acute abdomen but that in these cases laparotomy can often be avoided.

T43

Ileorectal anastomosis in the treatment of inflammatory bowel disease (IBD)

J C COOPER AND N S WILLIAMS *(University Department of Surgery, The General Infirmary, Leeds)* The place of colectomy and ileorectal anastomosis (C+IRA) in the surgical management of IBD remains controversial. In Crohn's colitis (CC) there appears to be a greater risk of recurrence whereas in ulcerative colitis (UC) there is the risk of malignant change.

The outcome of 59 patients who underwent C+IRA (1° anastomosis n=40; 2° anastomosis n=19) between 1955 and 1982 were reviewed. In all cases the macroscopic appearance of the rectum at the time of surgery was either normal or showed mild inflammation. Thirty seven operations were performed for CC (mean age 35± SEM 2 years; M:F 8:29) and 22 for UC (39± 3 years; M:F 8:14). Operative mortality was 8% for CC and 0% for UC. Seven patients (18·9%) with CC suffered a clinical anastomotic leak compared with three patients (13·6%) with UC. Nine of these ten patients had undergone a 1° anastomosis.

Overall follow up was 7·2±1 years, and at the time of review 11/30 patients (37%) with CC, and 6/19 patients with UC (32%) had undergone re-operation for recurrent disease. Cumulative re-operation rates at 10 years however were 76% and 73% respectively. No case of carcinoma of the rectum has occurred and the patients in both groups with an intact IRA enjoy good health with a stool frequency of 4-6/day.

The results suggest that the outcome of C+IRA in terms of recurrence is similar for UC and CC. Anastomotic leakage can be reduced by delayed anastomosis. Although the re-operation rate was high in both groups, many young patients avoided an ileostomy and pelvic nerve damage and remained in good health for several years.

As mucosal proctectomy with an ileal reservoir, the alternative sphincter saving procedure for the treatment of UC, is contra-indicated in Crohn's disease, we recommend C+IRA as first line surgical treatment for CC provided the rectum is minimally involved.

T44

Are there ethnic differences in inflammatory bowel disease in England?

A KESHAVARZIAN, S GUPTA, S H SAVERYMUTTU, AND H J F HODGSON *(Royal Postgraduate Medical School, Hammersmith Hospital, London)* Environmental, racial and familial facters are all relevant to the epidemiology of inflammatory bowel disease (IBD). Inflammatory bowel disease has been increasingly recognised in immigrants, however the magnitude of the problem, and relative proportion of immigrant patients residing in the UK having ulcerative colitis (UC) and Crohn's disease (CD) has not been studied. In this survey, we have determined the types of idiopathic inflammatory bowel disease present in patients of two immigrant groups of different racial background and compared them with Europids. Of the 250 patients attending a single IBD clinic 10·8% were Indian (from the subcontinent or East Africa) and 3·6% Caribbean. The proportion of immigrants in IBD clinic was similar to the chest and antenatal clinics in the same hospital. Among the Indians 78% had UC, 22% had CD. Among the West Indians 22% had UC, 78% had CD. Among Europids 42% had UC, 58% had CD. Ulcerative colitis was significantly more common amongst the Indian patients with IBD than the Europids ($\chi^2=12{\cdot}31$, $p<0{\cdot}001$) or the West Indians ($\chi^2=9{\cdot}03$, $p<0{\cdot}01$). In both immigrant groups similar high proportions (over 78%) of patients were non-smokers. The data indicate that IBD occurs in immigrant racial groups and the pattern differs between Indians and West Indians. Whether this reflects genetic, or environmental factors remains uncertain.

T45

Non-specific inflammatory bowel disease in immigrants: incidence and prevalence in the Midlands

E T SWARBRICK, R D MONTGOMERY, P W DYKES, R H GRACE, J A LLOYD, AND R N ALLAN *(New Cross and Royal Hospitals, Wolverhampton, and The East Birmingham and General Hospital, Birmingham)* While ulcerative colitis (UC) and Crohn's Disease (CD), are often thought to be uncommon in Asian and West Indian immigrants, experience in the West Midlands suggests otherwise. This study reports data on cases of UC and CD in immigrants from throughout the region collected by the Midland Gastroenterologial Society.

Eleven hospitals have contributed 126 patients to this study. One hundred and two were diagnosed as having UC, 24 as CD. Of the UC patients, 88 were Asian, 10 were West Indian and four were from other countries. The average number of years resident in the UK by first generation immigrants before developing symptoms was 11 (range 1-41). Of the CD patients, 19 were Asian, four West Indian and one was from another country. The average number of years spent in the UK by first generation immigrants before developing symptoms was 11 years (range 2-21).

In one centre, 150 new patients with UC and 66 with CD have been entered into a long term prospective study over a seven year period; of these 29 patients (13%), were of Indian or West Indian origin, 24 (16%) had UC, five (8%) had CD. The Indian and West Indian population is 15% of the total population. Furthermore, from estimated current prevalence rates of 80 per 10^5 population for UC and 30 per 10^5 for CD, 31 immigrants would be expected to have had UC and 12 CD; the observed figures were 38 and six respectively.

This study suggests that the prevalence and incidence of inflammatory bowel disease in the Indian and West Indian population is similar to the native population.

T46

Abnormal pulmonary function in ulcerative colitis

I M CHESNER, A WILLIAMS, J OSMAN, D E STABLEFORTH, AND P ASQUITH *(The Alastair Frazer and John Squire Metabolic and Clinical Investigation Unit, East Birmingham Hospital, Birmingham)* The association between non-smoking and ulcerative colitis (UC) remains unexplained but recently it has been suggested that UC is characterised by a change in smoking habit and that smoking may confer some protection against UC. The effect of pulmonary pathology in association with UC has never received consideration. We have therefore studied the pulmonary function and smoking habit of 52 unselected patients with UC compared with 57 age and sex matched controls with non-inflammatory bowel disease. Eight of 52 (15%) of UC patients were current smokers compared with 29/57 (51%) of controls ($p<0{\cdot}01$). However, 24/52 (46%) were ex-

smokers compared with 5/57 (9%) of controls ($p<0.01$) demonstrating that UC is associated with a change to non-smoking rather than life long non-smoking. There was no difference in the mean number of cigarettes smoked expressed as pack years, UC 22·8, controls 25.5. Airway obstruction ($FEV_1/FVC<65\%$) was found more frequently in UC's 7/52 (13%) compared with 1/57 (1·7%) in controls ($p<0.05$). Disease activity did not correlate either with airways obstruction or with current smoking habit.

In conclusion, this new finding of significant airways obstruction in association with UC may be an important factor in influencing the change in smoking habit of these patients.

T47

Role of intercurrent infections in acute exacerbation of chronic inflammatory bowel disease

H O KANGRO, S K F CHONG, R B HEATH, AND J A WALKER-SMITH *(Department of Virology and Child Health, St Bartholomew's Hospital, West Smithfield, London)* Between October 1981 and June 1983, 85 children with chronic inflammatory bowel disease (CIBD) were investigated serologically to determine the role of intercurrent virus infections as a cause of acute exacerbations. Altogether 151 episodes of acute onset gastrointestinal symptoms were recorded. There was no definite seasonal pattern, although peaks of incidence occurred during the winter months and in April/May each year, coincidentally with peaks of respiratory tract infection (RTI).

There was no difference in the prevalence of antibody to 11 viruses, *Mycoplasma pneumoniae, Chlamydia psittaci* and *Coxiella burnetti* between children with CIBD and 79 control children of similar age.

Follow up serum specimens were obtained from 72 of the children with CIBD and in these, 49 intercurrent infections were diagnosed during the study period. Twenty seven (55%) of these infections were caused by the respiratory viruses: influenza, parainfluenza and respiratory syncytial virus, and 22 were systemic infections. Altogether 20 (40·8%) infections – 10 respiratory and 10 systemic – were accompanied by acute gastrointestinal symptoms.

Our study shows that the frequency of intercurrent virus infections is not increased in children with CIBD. Such infections, however, are frequently associated with episodes of acute exacerbation of CIBD of which respiratory tract viruses account for the major proportion (40·8%).

T48

Specificity of ^{111}In-granulocyte scanning and faecal excretion measurement – an autoradiographic study

A KESHAVARZIAN, Y E PRICE, A M PETERS, J P LAVENDER, N WRIGHT AND H J F HODGSON *(Royal Postgraduate Medical School, Hammersmith Hospital, London)* ^{111}In-WBC scanning is now a well-established technique for diagnosis and assessment of inflammatory bowel disease (IBM). ^{111}-Indium is used to label granulocytes in vitro, and then cells are subsequently injected intravenously. The isotope localises in inflamed bowel and subsequently can be counted in faeces. The validity of the test in distinguishing cell loss from protein losing enteropathy critically depends on stability of granulocyte labelling. We have therefore investigated this, using an autoradiographic technique, in nine patients in whom ^{111}In granulocyte scan and colonoscopy were carried out simultaneously. ^{111}In autologous granulocytes were injected three to four hours before colonoscopy, and intraluminal fluid, mucosal brushings, and colonic biopsies were collected during the colonoscopic procedure. In two patients with no histological evidence of inflammatory bowel disease, and three with clinically and histologically inactive disease, no ^{111}In was detected in fluid, brushings or biopsies. In patients with active disease, 88% of the ^{111}Indium activity in colonic fluid was precipitated by low speed centrifugation. Autoradiography confirmed that the label remained attached to whole granulocytes in colonic fluid and mucosal brushings. Studies on biopsies, at intervals up to four and a half hours following labelled granulocyte injection, showed labelled neutrophils on the inflamed epithelial surface, with occasional neutrophils in crypt abscess by three hours. We conclude that the technique of ^{111}In-granulocyte scanning and faecal counting in patients with IBD are specifically measuring cell loss; labelled neutrophils are capable of migrating through the gastrointestinal mucosa, in active disease, within three hours of administration.

T49

Circulating IgA immune complexes in inflammatory bowel disease

H McKENZIE, J MAIN, D PARRATT, AND C R PENNINGTON *(Department of Bacteriology, Ninewells Hospital, Dundee and Department of Medicine King's Cross Hospital, Dundee)* IgA containing immune complexes have been shown in the sera of patients with inflammatory bowel disease (IBD) by means of a conglutinin binding ELISA assay. In 13 patients with Crohn's disease, the mean levels of IgG and IgA complexes respectively were 39 μg aggregated IgG equivalent/ml, range 13–105, and 76 arbitrary units IgA/ml, range 14–178. These were significantly higher than the corresponding values in seven control subjects of 16 μg aggregated IgG equivalent/ml, range 7–33, and 26 arbitrary units IgA/ml, range 9–44 ($p<0.01$, Mann-Whitney test). In seven patients with ulcerative colitis, mean levels of immune complexes were 23 μg of aggregated IgG equivalent/ml, range 10-65, and 57 arbitrary units IgA/ml, range 10-180. Gel filtration of selected Crohn's disease sera has shown that immune complexes measured by the conglutinin binding assay are heterogeneous in size, but that in general the IgA complexes are significantly larger than IgG complexes.

There have been many reports of raised levels of immune complexes in IBD, but there is little information available on their composition. Detailed analysis is essential to ensure that *in vitro* immunoglobulin aggregates do not produce false positive results. Our findings provide the first direct evidence of IgA involvement in immune complex formation in IBD, and it should be possible to establish whether the IgA is systemic or secretory in origin.

T50

Histopathological features of focal lesions in the jejunal mucosa in Crohn's disease are consistent with a cell-mediated immune response

J H ENTRICAN, A BUSUTTIL, AND ANNE FERGUSON *(Gastrointestinal Unit and Department of Pathology, Western General Hospital, Edinburgh)* Cell mediated immune responses in the small intestine are characterised by an increase in intra-epithelial lymphocyte numbers and in crypt length, with or without a reduction in villous length. With the introduction of peroral jejunal biopsy, minor non-specific abnormalities of jejunal mucosal architecture have been observed in Crohn's disease, however no formal measurements of crypt and villous length have been carried out. The intra-epithelial lymphocyte (IEL)

count in jejunal biopsies from patients with Crohn's disease has been reported to be normal.

A study of jejunal biopsies from 33 patients with Crohn's disease, in whom the sites of macroscopic disease were known, has revealed the presence of focal lesions in 10 biopsies. These focal abnormalities consisted of ulcers, fissures and granulomas, and their occurrence was independent of the presence of macroscopic jejunal disease. Comparison of the IEL counts and crypt and villous length measurements in Crohn's biopsies with and without a focal abnormality with biopsies from normal controls has been made. A highly significant increase in IEL count was found in those biopsies with a focal abnormality ($\bar{x}$=67·2 SEM=9·5 per 100 epithelial cells) compared to those without a focal abnormality ($\bar{x}$=32 SEM=1·7). Likewise a highly significant increase in crypt length occurred in those biopsies with a focal abnormality ($\bar{x}$=387 μm SEM=54·9) compared to those biopsies without a focal abnormality ($\bar{x}$=122 μm SEM=9·2). These findings are consistent with a local cell-mediated immune response at focal lesions in the jejunal mucosa in Crohn's disease.

T51

Lymphocyte transformation in inflammatory bowel disease – effect of the monocyte suppressor cell

D KELLEHER, A MURPHY, C FEIGHERY, C A WHELAN, P W N KEELING, AND D G WEIR *(Departments of Clinical Medicine and Immunology, Trinity College and St. Jame's Hospital, Dublin, Eire)* Previous studies have shown impairment of the cell mediated immune response in inflammatory bowel disease. Experiments using mixed populations of mononuclear cells have suggested reduced lymphocyte transformation.

To investigate the effects of the monocyte suppressor cell on lymphocyte transformation, we performed lymphocyte transformation studies in the presence and absence of indomethacin. The monocyte can suppress lymphocyte transformation by prostaglandin production, and the alteration in transformation induced by indomethacin allows calculation of the percentage monocyte induced suppression. The percentage monocyte count was also assessed using the MO_2 monoclonal antibody. In 21 patients with inflammatory bowel disease mean transformation with 5 μg/ml of Con A rose from 22641±10287 to 38807±12859 on addition of indomethacin ($p<.01$). There was no significant rise in transformation in controls by comparison (24842±13938 to 24570±13577). The mean percentage monocyte induced suppression calculated from these results are 42·6±20 for CIBD as against −7·62±36·7 for controls, a difference which is highly significant. Percentage monocyte count was also significantly elevated in patients (22±10%) *versus* controls 6±1·3%). There was a good correlation between percentage monocyte count and percentage monocyte suppression (r=0·81).

In summary, the reduction in lymphocyte transformation seen in inflammatory bowel disease appears to be mediated by the relative monocytosis seen in this condition. Pure lymphocyte transformation is in fact enhanced. The exacerbations of inflammatory bowel disease seen following therapy with anti-prostaglandin agents, such as indomethacin, may result from the lifting of monocyte induced suppression.

T52

Abnormal cell mediated immunity in inflammatory bowel disease

C C AINLEY, J CASON, R A WOLSTENCROFT, P W N KEELING, AND R P H THOMPSON *(The Gastrointestinal Laboratory, Department of Immunology, St Thomas' Hospital, London)* Abnormal cell mediated immunity (CMI) in inflammatory bowel disease (IBD) is controversial because limited individual studies use differing methods and patient groups. Cell mediated immunity was studied in detail in 27 patients with Crohn's disease (CD), 13 with ulcerative proctocolitis (UC) and 25 controls (CO).

Delayed hypersensitivity skin testing to four recall antigens was assessed as the sum of diameters of reactions. Peripheral blood lymphocytes (PBL) were counted and T cell populations estimated using OKT monoclonal antibodies. Peripheral blood lymphocytes transformation responses to graded doses of phytohaemagglutinin (PHA) and concanavalin A (Con A) were measured by tritiated thymidine incorporation in 72 hr cultures containing either 10% autologous or pooled AB plasma.

Skin reactions were reduced in CD and UC (CO: 48·5 mm±7·1, n=11, v CD: 20·5±4·3, n=21, $p<0·001$, and UC 25·4±4·0, n=11, $p<0·005$; mean±SEM). In CD and UC there was a small reduction in PBL counts. The percentage OKT3+ cells, and the OKT4+ ('helper') : OKT8+ ('suppressor') ratio were normal in CD, but in UC the ratio was reduced (CO 1·93±0·07, n=14, v UC: 1·12±0·19, n=9, $p<0·001$). Crohn's disease and UC PBL responses were reduced in AB plasma, but this was only significant for UC cells at a suboptimal dose of Con A (0·625 μgm/well), $p<0·05$. Crohn's disease cells required a higher concentration of Con A for peak response than CO (χ^2=10·2, $p<0·01$). In autologous plasma, peak responses of CD cells to both mitogens was reduced compared with AB plasma (PHA, $p<0·01$; Con A, $p<0·02$).

Cell mediated immunity is abnormal in IBD. In UC this appears to be due to an abnormal PBL OKT4 : OKT8 ratio. In contrast, in CD there is a qualitative cell defect and abnormal factors in plasma.

T53

Possible role for anti-idiotypic antibodies in Crohn's disease

C O'MORAIN, R JAEGER, AND K M DAS *(Albert Einstein College of Medicine, Bronx, NY, USA, and the Adelaide and Meath Hospitals, Dublin, Ireland)* Immunological mechanisms have been implicated in the aetiology and pathogenesis of Crohn's disease (CD). Idiotypic and anti-idiotypic antibodies (Id-anti-Id) have a role in autoimmune diseases characterised by remissions and exacerbations. The aim of this study was to see if Id-anti-Id occurred in Crohn's disease. IgG was purified from sera of healthy volunteers (n=12), Crohn's disease (n=15) and patients with ulcerative colitis (n=10). Antisera was raised in Balb/c mice against IgG from normal volunteers and Crohn's disease and ulcerative colitis patients. A radioimmunoassay was developed and standardised using IgG as the solid phase antigen antisera to IgG as the antibody and ^{35}S-labelled monoclonal mouse anti K chain as the second antibody. IgG from the three groups were coincubated with the antisera in a competitive binding assay. The control IgG inhibited bind by 42+7%, ulcerative colitis IgG by 38+8% and 11 of 15 patients with Crohn's disease IgG by 52+10%. Four of patients with Crohn's disease did not inhibit the binding at all and rather enhanced the binding by 10%. This was observed when the assay conditions were Crohn's disease IgG as the solid phase and antisera to that IgG as the antibody. These four patients had systemic manifestations of arthritis. All four sera were negative on latex agglutination and two were positive by C Iqbinding assay. The explanation of these results could be that patients with extraintestinal manifestations of arthritis have cir-

culating anti-idiotypic antibodies in the IgG fraction that cross-react with the IgG to enhance binding. Characterisation of the antibody would be important in the pathogenesis of Crohn's disease.

T54

Malnutrition, but not zinc deficiency, causes depressed cell mediated immunity in Crohn's disease

C C AINLEY, J CASON, B M SLAVIN, R A WOLSTENCROFT, P W N KEELING, AND R P H THOMPSON *(The Gastrointestinal Laboratory, Department of Chemical Pathology, Department of Immunology, St Thomas' Hospital, London)* Malnutrition, in particular zinc deficiency, may be important in the depressed cell mediated immunity (CMI) of Crohn's disease (CD). Cell mediated immunity was studied in detail in 27 patients with CD and related to their nutrition and zinc status.

Delayed hypersensitivity skin testing to four recall antigens was assessed as the sum of diameters of reactions. Peripheral blood lymphocyte (PBL) populations were estimated using OKT monoclonal antibodies. Peripheral blood lymphocyte transformation responses to graded doses of phytohaemagglutinin (PHA) and concanavalin A (Con A) were measured by tritiated thymidine incorporation in 72 h cultures containing either 10% autologous or pooled AB plasma. Nutrition was assessed from anthropometric measurements, plasma albumin and retinol binding prealbumin (RBPA). The zinc contents of plasma and separated peripheral blood polymorphonuclear and mononuclear leucocyte subpopulations were measured by atomic absorption spectrophotometry.

Fifteen patients were normal (N) and 12 malnourished (MAL), being <90% of ideal body weight. Albumin but not RBPA was reduced in MAL compared with N, $p<0.01$. The two groups were well matched for age, sex, drug treatment, and duration, activity and site of disease. Skin reactions were reduced in MAL 15.0 ± 5.9, n=11, v N 26.5 ± 6.6, $p<0.05$. Peripheral blood lymphocyte counts and T cell populations were similar in N and MAL. In AB plasma, MAL peak responses to PHA ($p<0.01$) and Con A ($p<0.01$) were reduced compared with N. In both groups, peak PBL responses were reduced in autologous plasma compared with AB plasma. While plasma and polymorphonuclear zinc was reduced in MAL, mononuclear levels were normal, and there was no relation between zinc levels and CMI.

Malnutrition, but not zinc deficiency, causes impaired CMI in CD.

PLENARY SESSION
T55–59

T55

A new gastroenterologist in a district general hospital and is there a need for more of them?

W R BURHAM *(Department of Gastroenterology, Oldchurch Hospital, Romford, Essex)* Thirty two senior registrars were appointed as consultant gastroenterologists between 1980 and 1982, often replacing a general physician. Analysis of discharge summaries and other records indicate the workload of one of these. The numbers of in-patients on the firm were similar before and after the appointment (1980; 802 admissions; 1982; 868 admissions), but the proportion with gastrointestinal conditions increased from 11% to 19%. This was because of an increase in referrals from all sources and some diagnostic transfer. For example, more patients were diagnosed as having pain of oesophageal rather than uncertain cause; when these two diagnostic groups were combined, a significant reduction was found in the number staying more than seven days (1980; 13 of 54: 1982; three of 48: $\chi^2=4.83$, $p<0.05$); this was perhaps related to the increased availability of endoscopy.

New outpatient attendances per month increased from 50 to 84 in two years; 96% were for gastrointestinal problems. Endoscopies performed increased by 14 times in three years to 1473 in 1983; 75% of these were abnormal. In 100 cases, the endoscopic and clinical diagnosis differed in 38% but only in 15% might this have resulted in serious problems. Limited facilities have impaired patient care. The gastroenterologist's work load was much greater than that stated in a recent report. This suggests that there may be an urgent need for more consultant gastroenterologists in the UK.

T56

Beck depression inventory screening of Gastro-intestinal outpatients

J D R ROSE, A H TROUGHTON, AND P M SMITH *(Department of Gastroenterology, Llandough Hospital, Penarth, S Glamorgan)* Although functional bowel disorders are known to be common, associated and treatable depressive illness is often overlooked. To determine the value of screening and the incidence of depression as indicated by the self-administered Beck depression inventory (BDI), 110 consecutive referrals to a gastro-intestinal/general medical clinic completed the inventory – 100 satisfactorily. Alternate BDIs were retained unseen as controls. From a maximum score of 39, nine patients scored more than 16 (severe depression), 20 from eight to 15 (moderate), 21 from five to seven (mild) and 50 less than five (normal). The highest score was 30. Appropriate investigation failed to reveal organic disease in 33 of the 50 depressives (66%), two thirds of whom presented with abdominal pain or symptoms of irritable bowel syndrome. The BDI diagnosis of depression was disregarded in 13 patients, nine of whom were only mildly depressed and eight of whom had associated organic disease. Sixty six per cent of the severe depressives were, however, correctly diagnosed and appropriately treated, 55% of the moderate and 29% of the mild. No normal patient was given anti-depressants. Knowledge of the BDI score increased the diagnosis from 8/22 (36%) to 16/28 (57%).

The BDI showed that half of new outpatients were depressed and the majority of these had no other organic disease.

T57

Cholecystectomy rates in the United States and the United Kingdom compared: does the difference matter?

T BATE, P J GODFREY, M HARRISON, B WALSH, AND D H LEVIEN *(William Harvey Hospital, Ashford, Kent. New Rochelle Hospital Medical Centre, New York, USA)* Cholecystectomy rates are higher in N America than the UK and this may be partly due to an increased prevalence of gall stones. If, however, there is a real difference in surgical practice, what is the consequence?

We have compared two necropsy series, one from a US suburban hospital and the other from a partly rural UK health district in which the biliary tract was specifically examined in each case for gall stones (A) or a cholecystectomy scar (B). In the US series of 1000 subjects, gall stone disease (A+B) was found in 33% of women and in the UK series of 1701, 24%. The male prevalence of gall stones was 20% in the US series and 12% in the UK series. The cholecystectomy

rates for those with gall stone disease (B/A+B) for women were, however, US, 39% *versus* UK, 15% and for men, US, 35% *versus* UK 5%. The overall cholecystectomy rate was 5½ times greater in the US series and, even allowing for the higher prevalence of gall stones, was still 3½ times the rate in the UK series. There were 11 gall stone related deaths in US series (1.1%) of which six were postoperative, compared with 10 such deaths in the UK series (0·6%) of which four were postoperative. The operative mortality for cholecystectomy in the US hospital was 2·2% and in the UK district was 1·1%.

Neither the hospitals nor the populations served are strictly comparable. We found no evidence, however, to support the idea that a higher cholecystectomy rate leads to a lower operative mortality and therefore a lower overall death-rate from gall stone disease. It is concluded that there is no demonstrable advantage to be gained from increasing the present cholecystectomy rate in the United Kingdom.

T58

Symptom duration and pathologic staging of colorectal cancer

R S STUBBS AND M G LONG (introduced by PROFESSOR L H BLUMGART) *(Hillingdon and West Middlesex University Hospitals, Middlesex)* Delays in diagnosis are often felt to be responsible for the late presentation and hence poor prognosis seen in so many patients with large bowel cancer. The present prospective study examines the duration of symptoms and stage of disease in 211 consecutive patients with colorectal cancer. Patients were allocated to one of four groups according to the duration of symptoms; 0-3 months, 3-6 months, 6-12 months, and over 12 months. Tumours were staged according the Dukes classification with the addition of stage D to include those patients with distant metastases. Four patients could not be staged. The mean ± SE duration of symptoms for Dukes A patients was 11·2±2·6 months; for Dukes B patients 4·9±0·6 months; for Dukes C_1 patients 5·3±0·7 months; Dukes C_2 patients 3·9±1·9 months, and for Stage D patients it was 3·8±0·6 months. In summary there was no tendency for a longer symptomatic period in patients with late stage disease. Indeed the reverse was the case. Dukes A patients had a significantly longer duration of symptoms than Stage D patients ($p<0·01$). In the light of current knowledge concerning tumour growth relatively few patients could be expected to have been detected at an earlier stage of disease by more prompt diagnosis.

Delay in diagnosis does not appear to be a major contributing factor to the all too frequent late presentation of colorectal cancer. It would seem the key to diagnosis at an earlier stage of the disease must rest with presymptomatic detection.

T59

Changes in the surgical management of ulcerative colitis

D G NASMYTH, D JOHNSTON, AND N S WILLIAMS, *(University Department of Surgery, The General Infirmary, Leeds)* Mucosal proctectomy (MP) or intersphincteric dissection (ISD) permit the eradication of rectal disease in ulcerative colitis (UC) without the risk of damage to pelvic nerves. After mucosal proctectomy, gastrointestinal continuity may be restored by ileo-anal anastomosis (IAA) with or without a pelvic reservoir (RES). The impact of these procedures on surgery for UC is presented in a consecutive series of 80 patients who underwent their first operation for UC between 1977 and 1984.

Thirty three (41%) cases were emergencies and the rectum was conserved in 29 (88%), 22 (67%) underwent subsequent elective surgery. Of the 80 patients, 25 (31%) underwent MP+IAA+RES, 6 (8%) MP+IAA, 5 (6%) MP+caeco-anal anastomosis, 19 (24%) MP/ISD+ileostomy, 5 (6%) panproctocolectomy, 10 (12·5%) ileorectal anastomosis, and in 10 (12·5%) the rectum was defunctioned.

The results of IAA+RES are good in 19 (86%) after restoration of gastrointestinal continuity. The mean frequency of defaecation is 5–8/24 hours. All patients evacuate spontaneously without intubation and 75% can defer defaecation for over 30 minutes. Overall the functional results of IAA were better with a reservoir.

The operative mortality was 0% in elective and 6% (n=2) in emergency cases. Twenty four per cent (n=6) of IAA+RES underwent re-operation for early complications, and 16% (n=4) for late complications, compared with 23% (n=8) and 15% (n=5) where gastrointestinal continuity was not restored. No bladder or sexual dysfunction has been reported. Hence both mucosal proctectomy and intersphincteric dissection are safe and preferable to panproctocolectomy in the surgical treatment of UC. Preservation of the rectum is recommended in emergencies, and restoration of gastrointestinal continuity should be considered in all elective operations.

COLORECTAL
F1–8

F1

Early detection of carcinoma in sigmoid diverticular disease

A COWIN, D G KARAMANOLIS, P B BOULOS, P R SALMON, AND C G CLARK *(Department of Surgery, Faculty of Clinical Sciences, University College London, and The Rayne Institute, London)* The sigmoid colon is a common site for diverticular disease and neoplasia but the frequency of their coexistance is not clear. With increasing frequency of colonic cancer, precision in diagnosis is necessary but radiological diagnosis has its limitations because of the difficulty in outlining the mucosa in the presence of diverticulae. This study therefore investigates this clinical problem.

In 105 symptomatic patients reported to have sigmoid diverticulae on barium enema, colonoscopy was performed. There were 42 men and 64 women whose age medians and ranges were 72 (47–85) and 68·5 (45–89) years respectively. In 31 patients (group A) the barium enema showed polyps in 29 and carcinoma in two but colonoscopy confirmed polyps in 11 and excluded the others. In 74 patients (group B) the barium enema showed diverticular disease alone but colonoscopy revealed polyps in 22 and carcinoma in three. The polyps were adenomas and in two patients in each group were malignant graded Duke's A. The carcinomas were Duke's B in two and Duke's C in one.

Therefore 36 (34%) patients had coexistant neoplasia, benign in 29 (27·6%) and malignant in seven (6·6%). The peak age incidence was 60–80 years with a 3:1 female to male distribution; five carcinomas were in women and two men. Similar number of patients had abdominal pain or change in bowel habit as in the remaining 69 patients without neoplasms but 22 with and 26 without neoplams had rectal bleeding ($p<0·025$).

This study shows that patients' symptoms are not diagnostic and as the barium enema was inaccurate in 45 (43%) examinations, routine colonoscopy or flexible sigmoidoscopy is desirable but such a policy is demanding. The results suggest that it is

probably essential in patients more than 60 years especially women and definitely all those with rectal bleeding.

F2

Sigmoidoscopy/proctoscopy service with open-access to general practitioners

I P DONALD, J S FITZGERALD FRAZER, AND S P WILKINSON *(Gloucestershire Royal Hospital, Great Western Road, Gloucester)* Many hospitals now offer barium enema examinations to general practitioners (GPs) on an open-access basis thus bypassing the traditional sequence of first carrying out a sigmoidoscopy. An open-access sigmoidoscopy service was therefore opened with requests for a barium enema not being accepted without prior sigmoidoscopy.

During the first three and a half years 1458 patients referred directly from their gp were examined using a rigid sigmoidoscope. The patient was also examined with a proctoscope if thought appropriate. After the first year of the service a subsequent examination with a fibreoptic sigmoidoscope was also carried out if the presenting symptom was bleeding and no cause for this found with the rigid instruments.

Five hundred and sixteen abnormalities were found to account for the patient's symptoms in 506 patients, giving a diagnostic rate of 35%. The most common was piles (307 cases). Other relatively common pathologies included inflammatory bowel disease (107), benign tumours (44) and malignant tumours (38). Of 41 patients subsequently undergoing fibreoptic sigmoidoscopy a cause for the bleeding was found in 32 the most common being a malignant tumour (16).

Most gps in the district have used the service and a questionnaire survey indicated the majority to have fallen by almost two-thirds with the waiting time falling from up to nine months to only two weeks.

F3

Abnormal sacral spinal cord function in chronic idiopathic constipation

J S VARMA AND A N SMITH *(University Department of Surgery/Urology, Gastro-Intestinal Wolfson Laboratory, Western General Hospital, Edinburgh)* The function of neurones within the sacral spinal cord (SSC) is essential for the normal mechanisms of defaecation. This site also mediates a polysynaptic sacral evoked response (SER) which can be elicited by stimulation of the dorsal nerve of the penis or clitoris and recording reflex contraction of the external anal sphincter. We have utilised the presence and latency of the SER as an index of SSC function in 14 patients with chronic idiopatic constipation and compared the data with 22 asymptomatic age-matched control subjects. All the constipated patients had investigations to exclude organic or systemic disease and none had previous abdominal surgery. Anal sphincter manometry was also performed to measure functional sphincter length, resting and squeeze pressures and the recto-sphincteric reflex. The dorsal nerve of the penis and clitoris was stimulated electrically using a surface electrode (duration 0.1 msec, frequency 2Hz, voltage 3 to 4 times sensation threshold). Over 100 anal sphincter responses were detected by a bipolar surface platinum anal plug electrode and the digitally averaged response recorded. The procedure was repeated for each subject. Reproducible responses were confirmed in all cases. The control group had a latency range of 27·2–47.6 msec (mean 37·3±1·4 SEM). In contrast two patients in the constipation group had an absent SER, the remainder having a latency range of 39·6–65·2 msec (mean 51·2±2·2 SEM). The prolongation of the SER latency in the constipation group is significant ($p<0·01$; Wilcoxon's rank sum test). Sensation threshold and anal sphincter manometry did not show any significant differences between the two groups.

These abnormalities of the SER in the presence of normal peripheral sensation and anal sphincter function suggest an occult neurogenic dysfunction of the SSC in some cases of chronic idiopathic constipation.

F4

Development of a rational surgical policy for the management of radiation–induced gastro-intestinal lesions

R B GALLAND AND J SPENCER *(Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London)* Sixty patients (13M, 47F) presented with radiation–injured gut between 1958 and 1984. The median age at receiving radiotherapy (RT) was 54 years. Radiotherapy was performed mainly for gynaecological (43) or urological (14) malignancy. External RT was used in all cases, combined with internal treatment for cervical cancer. Eighty four gastrointestinal lessions were produced (11 being synchronous and 13 metachronous). There were 53 strictures, 14 fistulae, nine perforations and eight bleeds. The period between RT and clinical manifestation of the lesion was approximately two years and was longer for strictures than for the other lesions. The majority of the lesions were in the rectosigmoid (39) or mid and distal small bowel (34). Forty nine patients required one or more operations and review of the operative results up to 1977 showed a high incidence of anastomotic leak and death after resection and primary anastomosis. We noticed, however, that the ascending, transverse and descending colons were relatively free of radiation-induced disease. Since then we have used a non-irradiated part of the colon for one end of the anastomosis. Thus terminal ileal resection has been followed by an ileo-transverse anastomosis and rectosigmoid resection by mobilisation of the splenic flexure to bring the descending colon down for anastomosis. Using these techniques there has been one leak in 12 anastomoses and none of the 11 patients have died. These results are significantly better ($p<0·05$) than our previous figures when 12 of 24 amastomoses leaked with 10 deaths.

We conclude that use of non-irradiated bowel for one end of an anastomosis significantly improves the results of resection of irradiated bowel.

F5

Is the balloon expulsion test a valid measure of the pelvic floor abnormality in slow transit constipation?

A M ROE, D C C BARTOLO, J VIRJEE, AND N J McC MORTENSEN *(Departments of Surgery and Radiodiagnosis, Bristol Royal Infirmary, Bristol)* Some patients with slow transit constipation (STC) have a pelvic floor abnormality. It has been suggested that a ballon expulsion test is a useful measure of this disorder.

We have studied 12 patients (11F, 1M) with STC (defined radiologically) and 16 controls. After anorectal manometry, changes in the anorectal angle and perineal descent on straining were measured on proctograms and compared with the patient's ability to expel a 50 ml water-filled balloon from the rectum. There were eight patients who could not (group A) and 4 who could (group B) expel the balloon. All controls tested could expel the balloon.

There was no significant difference in resting anal pressure between controls and group A or B. Medians and ranges were

controls 80 (60–105) cmH_2O, group A 113 (60–145), group B 100 (85–120). Anorectal angle significantly increased on straining in controls but did not in group A or B. Mean measurements in degrees at rest and on straining were controls (n=11) 91·4±6.7 and 108·1±13·7 (p<0·005); group A 100·3±11·6 and 96·1±13·6 (p=NS); group B 93·3±17·3 and 90·8±18·6 (p=NS). There was no significant difference in perineal descent on straining between controls and group A. Perineal descent, however, was significantly greater in group B than controls and group A. Medians and ranges in cm below the pubococcygeal line were controls 1·7 (0·9–4·3), group A 1·5 (0·4–2·1) and group B 3·2 (2·8–3·7) (p<0·02 compared with controls and p=0·002 compared with group A). Proctogram showed small rectocoeles in three of the four group B patients.

We conclude that inability to expel a balloon from the rectum is a reflection of a pelvic floor disorder in which STC patients fail to increase the anorectal angle on straining. When there is significant perineal descent, however, the test may be misleading. Proctograms give a more accurate indication of the dynamics of the pelvic floor disorder.

F6

Intraoperative staging of rectal cancer by imprint cytology

S H SILVERMAN, JANET MOORE, H THOMPSON, AND M R B KEIGHLEY *(Departments of Surgery and Pathology, General Hospital, Birmingham)* Restorative anterior resection for locally advanced tumours may be followed by recurrence around the anastomosis necessitating later A-P resection or defunctioning colostomy. Subjective assessment of invasion of glands or perirectal tissue by the surgeon can be misleading. Intra-operative pathological examination of the tumour bed and local lymph nodes would allow a more rational decision on the type of resection to be performed.

After tumour mobilisation, biopsies from the pelvic side walls, C_1 and C_2 lymph nodes were examined by imprint cytology and subsequently by paraffin section histology. The result of cytological examination was available within 15 minutes. Fifty two biopsies (23 nodes and 29 pelvic side wall tissues) were examined. Cytology and histology concurred in 48. In three (one node, two pelvic side wall tissue) malignant cells were seen cytologically but histology was negative. From previous experience we feel these are true positives for cytology. One further biopsy was a false negative for cytology, malignant tissue being seen histologically.

Intraoperative cytology can accurately assess lateral spread of rectal cancer and also determine lymph node status.

F7

A clearance technique for the detection of lymph nodes in colorectal cancer

S J CAWTHORN, N M GIBBS, AND C G MARKS *(The Royal Surrey County Hospital, Guildford, Surrey)* Lymph node metastases are the most important determinant of prognosis after surgery for rectal cancer. A minimum number of lymph nodes must be identified in each specimen for accurate staging of the tumour. In Guildford, a zylol/alcohol clearance technique is used to identify lymph nodes. We report a comparison between the numbers of lymph nodes obtained from the mesorectum of patients undergoing a randomised trial of pre-operative radiotherapy at Guildford (n=51), St. Mark's (n=50) and eight other centres (n=221). The total number of lymph nodes found in the Guildford series (mean =23·1±1·18 SEM) was significantly higher than St.Mark's (m=10·9±0·86) and the other eight centres combined (m=11·65± 0·4) (p<0·001). The total number of lymph node metastases was also significantly higher in the Guildford patients (m=3·21 ± 0·58) when compared with the combined eight centres (m=2·09±0·2) (p<0·05). The distribution of lymph nodes was examined by dividing the mesorectum into four zones, and a significantly higher number of lymph nodes were found in each zone of the Guildford patients. When the number of lymph nodes involved by tumour were compared, these were significantly raised in the lowest (supra-levator) zone (m=1·2±0·4) compared with St. Mark's (m= 0.13±0·1) and the eight centres combined (m=0·4± 0·1). Using this clearance technique, we have detected increased numbers of lymph nodes finding more involved by tumour in the supra-levator region of the mesorectum, a feature know to correlate with poor prognosis.

F8

Clinical importance of mucinous carcinoma of the large bowel

H C UMPLEBY AND R C N WILLIAMSON *(University Department of Surgery, Bristol Royal Infirmary, Bristol)* Mucinous carcinoma of the large bowel is reported to be associated with reduced survival compared with non-mucinous carcinoma. Over a seven year period there were 669 new patients with colorectal cancer of known histological type; 93 (14%) had mucinous tumours. The pathological features and outcome of mucinous and non-mucinous carcinomas were compared. A higher proportion of patients with mucinous compared with non-mucinous tumours were <40 years old (5% *vs* 2%:NS). The proportion of mucinous tumours occurring in the right colon was greater than non-mucinous tumours (27% *vs* 14% p<0.01), whereas the opposite held in the rectum (31% *vs* 46%: p<0.01). More mucinous than non-mucinous tumours were incurable at presentation (41% *vs* 28%: p<0·02). Polypoid adenomas were more often associated with mucinous than non-mucinous tumours (32% *vs* 22%:NS). Six per cent of mucinous carcinomas were multiple compared with 3% of non-mucinous cancers. Tumour resection rates were lower for mucinous than non-mucinous carcinomas, both overall (83% *vs* 92%: p<0·02) and 'curative' (61% *vs* 72%: p<0.05). Five year survival rates, however, were similar both overall (29 and 37%) and after 'curative' resection (53% and 57%). Mucinous tumours of the right colon had better five year survival rates, than at any other site (42% *vs* 17—30%). In Dukes' C tumours treated 'curatively' five year survival rates were better for mucinous that non-mucinous tumours (37% *vs* 28% NS).

The outcome of mucinous colorectal carcinomas is similar to 'ordinary, carcinomas. The high proportion of advanced cases at presentation seems to be balanced by the tendency for lymph node metastases to remain localised for a longer time.

OESOPHAGEAL/GASTRIC

F9—18

Is a columnar-lined (Barrett's) oesophagus reversible with medical treatment?

C J STODDARD, JANE E PATTERSON, AND D FLOOK *(Department of Surgery, University of Liverpool, Liverpool)* A columnar lined oesophagus (CLO) develops as a consequence of gastro-oesophageal reflux (GOR) and predisposes to the development of an oesophageal adenocarcinoma. The role of medical treatment in reversing this epithelial change is unclear.

Twenty patients (16 men, four women) with a diagnosis of CLO, based on endoscopic and histological examination, were treated with routine anti-reflux measures, ranitidine 150 mg bd, metoclopramide 10 mg tds and Gaviscon 10 ml qds for 12 months. Oesophageal manometry and 24 hour pH studies were performed before the start of treatment. Patients were seen at three monthly intervals for symptomatic review and repeat endoscopy and oesophageal biopsy. At each endoscopy the distance of the squamocolumnar junction from the incisor teeth, presence of oesophageal ulcers and strictures and position of the gastro-oesophageal junction were carefully determined.

Initially, all patients had GOR symptoms, 19 had a hiatus hernia, 10 an oesophageal ulcer and six an oesophageal stricture. Gastro-oesphageal reflux symptoms and dysphagia improved in 19 patients. Oesophageal ulcers healed completely in seven patients and only two needed a stricture dilating more than once. There was no evidence of significant mucosal regression in any patient. Thus this treatment regimen gives symptomatic improvement but does not lead to mucosal regression. There is no evidence that medical treatment causes mucosal regression in patients with a CLO.

F10

Gastrointestinal hormone release and gastric emptying in reflux oesophagitis

B J COLLINS, R J MCFARLAND, K D BUCHANAN, AND A H G LOVE *(Department of Medicine, The Queen's University of Belfast and Royal Victoria Hospital, Belfast)* Delayed gastric emptying has been recognised recently in patients with reflux oesophagitis but its mechanism has not been studied. Several gastrointestinal hormones including gastrin, neurotensin, and gastric inhibitory polypeptide (GIP), have been shown to influence gastric motility when infused intravenously. Vagal action is an important regulator of gastric emptying and pancreatic polypeptide (PP) blood concentrations provide a crude index of vagal activity. Thus, we have observed the release of glucose, insulin, gastrin, neurotensin, GIP and PP after a test meal of beefsteak pieces, potato, and orange juice during gastric emptying studies in patients with erosive reflux oesophagitis. Fifteen patients and 15 age and sex-matched control subjects were studied. Technetium-99m sulphur colloid labelled chicken liver (8 g) was used to label the solid portion of the meal and Indium-113m DTPA to label the liquid portion. Gastric emptying was measured for 90 minutes by a fixed scintillation detector and blood samples for hormone analysis were taken basally and at 15, 30, 60 and 90 minutes after meal ingestion. Emptying index values for solid and for liquid components of the meal were significantly smaller in patients than in control subjects, indicating a delay in gastric emptying in the patient group ($p < 0.01$) (Wilcoxon's signed rank test). An analysis of variance, however, detected no evidence of abnormal release of glucose, insulin, gastrin, neurotensin, GIP or PP in the patient group. We conclude that gastric emptying of solid and liquid components of a meal is delayed in patients with erosive oesophagitis but we have found no evidence for a hormonal or vagal mediated mechanism for the motility disturbance.

F11

Importance of upright and postprandial reflux in gastro-oesophageal reflux disease

J S DE CAESTECKER, J N BLACKWELL, JOAN BROWN, AND R C HEADING *(Department of Therapeutics and Clinical Pharmacology, Royal Infirmary, Edinburgh)* Fifty two patients underwent 23 hour ambulatory intraoesophageal pH monitoring using a naso-oesophageal probe with its tip sited 5cm above the distal end of the lower oesophageal sphincter. Recordings were made on a modified Holter portable recorder. Twenty nine patients were being investigated for suspected gastro-oesophageal reflux and 23 for recurrent chest pain. All patients were endoscoped and oesophagitis was detected in 29.

The acid exposure time was calculated as the proportion of time with pH<4. Total exposure time correlated well with upright (daytime) and supine (night-time) exposure ($r=0.88$ and 0.76 respectively), though there was a poor correlation between the latter two ($r=0.48$). Exposure during the three hour period after the evening meal was calculated for each patient, and correlated well with the total exposure time ($r=0.76$). Although longer acid exposures were broadly associated with the presence of oesophagitis, 11/29 patients with oesophagitis had minimal supine reflux (exposure time <5%) compared with 3/29 in both the upright and three hour post prandial studies. Minimal supine and post prandial reflux (<5% exposure time) predicted the greatest number of patients without oesophagitis (16/23 and 14/23 respectively) compared with minimal upright exposure (8/23) and total exposure (10/23). When marked reflux in each period (exposure times >20%) was seen, the three hour postprandial recordings predicted more patients with oesophagitis (17/29) than the supine (8/29) or upright measurements (10/29).

The results indicate that upright reflux correlates at least as well as supine reflux with total acid exposure. A short period of pH monitoring after a meal may be an adequate predictor of the degree of acid reflux demonstrable in a 24 hour monitoring period.

F12

Normal gastro-oesophageal reflux patterns in young and middle-aged control subjects

B J COLLINS, R A J SPENCE, T G PARKS, AND A H G LOVE *(Departments of Medicine and Surgery, The Queen's University of Belfast, Belfast)* Abnormal gastro-oesophageal reflux is best detected by prolonged intraoesophageal pH monitoring. Published control data with this technique are limited, however, and no studies have assessed the influence of age on normal reflux patterns. We have monitored oesophageal pH for at least 16 hours in 13 young asymptomatic subjects, mean age 22 years, age range 19–30 years, and in 14 middle-aged asymptomatic subjects, mean age 49 years, age range 39–61 years. A pH sensitive radiotelemetry capsule and a portable receiving system were used for ambulatory monitoring, but all studies were conducted during an overnight hospital stay so that activity of the volunteers could be standardised. Data were analysed for frequency and duration of daytime (erect) and nocturnal (supine) reflux episodes. When reflux was defined as a fall in pH to <4 pH units young subjects experienced 0·235 (0·08–0·58), median (range), daytime episodes/h, and 0·1 (0–0·92) nocturnal episodes/h. Cumulative duration of the daytime episodes was 1·3 (0·3–3·8) min/h and the nocturnal episodes, 0·15 (0–1·9) min/h. Middle-aged subjects experienced 0·305 (0·07–0·71) daytime reflux episodes/h and 0·115 (0–0·26) nocturnal episodes/h. Duration of their daytime episodes was 1·98 (0·42–3·21) min/h and the nocturnal episodes, 0·19 (0–4·43) min/h. No statistically significant difference was detected between young and middle-aged subjects for either frequency or duration of daytime or nocturnal reflux episodes (Mann Whitney U test). Definition of a reflux episode as a

fall to pH <5 or pH <3 units, or as a drop in pH >2 pH units, did not alter the results of the comparison between the groups. We conclude that young and middle-aged control subjects have similar erect and supine reflux patterns and it is acceptable to use young volunteers to establish normal values in reflux studies of young and middle-aged patients.

F13

Gastro-oesophageal reflux (GOR) in patients with chronic duodenal ulcer (DU)

D FLOOK AND C J STODDARD *(Department of Surgery, University of Liverpool, Liverpool)* Gastro-oesophageal reflux (GOR) symptoms have been reported in 40% and oesophagitis in 26–68% of pre-operative duodenal ulcer (DU) patients, yet DU patients are rarely investigated or treated for coexistent GOR. After vagotomy, symptoms of GOR are less common but the prevalence of oesophagitis and the extent of GOR have not been quantified.

Fifty patients with DU were admitted for detailed symptomatic enquiry, endoscopy with oesophageal biopsy, oesophageal manometry and 24 hour pH study before elective surgery. The tests were repeated three months postoperatively and the results compared.

Before and after vagotomy, respectively, 50% and 12% of patients had symptoms of GOR, 30% and 32% had evidence of oesophagitis, 18% and 14% had a low value for lower oesophageal sphincter pressure and 58% and 48% had an abnormal pH study.

We conclude that GOR and oesophagitis are common in patients with chronic DU, and that although symptoms of GOR are lessened by vagotomy, there is no evidence of a reduction in levels of GOR or in the prevalence of oesophagitis.

F14

Ambulatory oesophageal pH monitoring: correlation of computerised interpretation of acid reflux with endoscopy

W G CHEADLE, G C VITALE, S A SADEK, AND A CUSCHIERI *(University Department of Surgery, Ninewells Hospital and Medical School, Dundee, Scotland)* A computerised system for ambulatory oesophageal pH monitoring was used in the evaluation of 111 patients and 35 volunteers. A pH-sensitive radiotelemetry pill or probe was positioned 5cm above the lower oesophageal high pressure zone. Oesophageal pH was recorded in the memory of a portable microprocessor. Computer programmes for interpretation of the oesophageal pH record allowed rapid comparison of each patient with the cohort of volunteers. Two analyses were used in both the erect and supine position. The reflux event analysis calculated number and duration of reflux events, and the total time pH <4, and the cumulative acid exposure analysis calculated percentage of all data points below pH 3,4, and 5.

Patients were divided into three groups for the purpose of comparison with endoscopic findings. Group 1 (n=69) consisted of patients with classic reflux symptoms, group 2 (n=16) those with predominant abdominal pain and mild reflux symptoms, and group 3 (n=26) those with previous gastric operations. Endoscopy was done in all patients and classified as normal, oesophagitis, or presence of stricture. The Mann-Whitney U test was used to compare groups of patients and volunteers. There was a stepwise increase in all parameters of reflux using both analyses which were all significantly greater than the volunteer values ($p<0.05$), and this corresponded to the endoscopic severity of inflammation. A positive pH monitoring test was defined as one in which any reflux parameter fell outside the mean plus 3SD of the 35 volunteers. Seventy three per cent of patients in group 1 had positive tests, and 87% were identified as acid refluxers using both endoscopy and pH monitoring. Sixteen patients in groups 2 and 3 had normal endoscopic findings, yet were identified as acid refluxers on pH monitoring. This study has shown the complimentary nature of these tests, and that pH monitoring especially identifies those patients with early or quiescent gastro-oesophageal reflux disease not seen on endoscopy.

F15

Comparison of radiotelemetry with gastric aspiration in the measurement of 24 hour intragastric acidity

J R REYNOLDS, J P WALT, J D HARDCASTLE, A G CLARK, H L SMART, AND M J S LANGMAN *(Departments of Surgery and Therapeutics, University Hospital, Nottingham)* Hourly gastric aspiration has commonly been used to assess the efficacy of antisecretory compounds. Intragastric electrodes have not generally been used because of fears regarding accuracy in the presence of food. We have compared continuous ambulatory 24 hour pH monitoring using a radiotelemetry capsule (RTC) with standard nasogastric aspiration over 24h. Eight studies were performed on four male duodenal ulcer patients in remission receiving either placebo or an antisecretory agent. At 0800h a 10FG Salem sump nasogastric tube was passed and the RTC was swallowed and fixed at 52 cm from the teeth. Gastric aspirates were taken half-hourly for the first five hours and then hourly until 0800h the next day. The pH of aspirated samples was measured immediately using a glass electrode. Continuous RTC pH was stored using a Medilog recorder. The pH measurements of gastric contents were compared with the RTC recordings at the same times. One hundred and eighty seven paired pH recordings were analysed. A significant correlation was found between RTC and aspirate pH measurements (Spearman correlation coefficient =0·9, $p<0.01$). No significant difference was found between median aspirate pH and median RTC pH for each individual (Mann-Whitney U test). Radiotelemetry measurements clearly showed the onset of action of the antisecretory drug (median 18, range 17–19min) and the buffering effect of meals. This cannot otherwise be shown without very frequent aspiration. Radiotelemetry pH monitoring is as good as gastric sampling in the measurement of 24h intragastric acidity. It allows continuous measurement of pH during normal acitivity without the supervision required when using repeated aspiration. This technique accurately assesses the effect of drugs on gastric acidity.

F16

Modified sham feeding: a measuring jug ward test for completeness of vagotomy

A C ATHOW, A T SEWERNIAK, T P BARTON, M R LEWIN, AND C G CLARK *(Department of Surgery, University College London, The Rayne Institute, London)* Sham feeding has been advocated as an alternative to the insulin test, as a check of completeness of vagotomy because of its safety and speed.

In studies on 22 normal subjects and of 33 preoperative patients with duodenal ulcer, volume responses to modified sham feeding for 15 minutes were equivalent to those of insulin (0·2 IU/kg bw) despite the fact that insulin at this dosage was a more powerful stimulant of acidity. Similarly, when 28 postoperative patients were studied volume responses were found to be as great to MSF as to insulin, although the mean PAO_{sh} was significantly lower than PAO_I. Thus peak

Vobs and peak V_G to sham were found to be as discriminatory in the diagnosis of RU as PAO_I and peak V_G to insulin. In six patients results of MSF and insulin testing gave opposite verdicts, in three MSF indicated incompleteness and three insulin tests indicate likewise.

These results suggest that MSF is as efficient as the insulin test. In addition to its other advantages, volume measurements alone are all that is required, making this a simple ward test.

F17

Instability of pepsin in stored gastric juice – a cause for concern?

D W BURGET, C J DE GARA, AND R H HUNT *(Intestinal Disease Research Unit, McMaster University, Hamilton, Ontario, Canada)*
Reported variations in studies of pepsin secretion may be because of the use of different assay methods or their application. Of especial concern are differing reports on the effects of storage conditions on pepsin measurement. We present the results of our experiments which aim to clarify the effects of time, temperature, and pH on pepsin stability.

Gastric juice specimens (n=36) were collected from normal volunteers during a basal period, and after pentagastrin administration. Each sample was divided into four portions which were left at the ambient pH of collection or adjuted to pH values of 1.0, 4.0, 6.0. Samples were then stored at either 4°C or –70°C and the resulting 1440 aliquots removed at intervals for pepsin assay by the bromophenol blue-albumin kinetic method.

A dramatic loss of peptic activity was observed in samples stored frozen at low pH, irrespective of whether the low pH was ambient or adjusted to pH 1 following collection. After one day of storage at −70°C, percentage of peptic activity remaining was 27 ±38 in samples frozen at ambient pH, 0.2±0.7 at pH 1, 99±16 at pH 4, and 97±13 at pH 6. Similar results were obtained on assay after storage at –70°C for 2, 3, or 7 days. There was complete loss of actlvity in ambient samples frozen at pH less than 1.4, and negligible loss in samples frozen at pH above 2·2. At intermediate pH, partial loss of activity on freezing correlated with pH. After 28 days of storage at −70° loss of activity was seen at pH 4·0. Percentage of peptic activity remaining was 15±35, 0±0, 65+43, and 101±16 at ambient pH, pH 1, pH 4, and pH 6 respectively.

Storage at 4°C showed no loss of activity for up to three days, but longer storage caused significant loss of activity when the pH was below 1·2. The percentage of peptic activity remaining after 28 days of storage at 4°C was 99±35 at ambient pH, 75±13 at pH 1, 124±24 at pH 4, and 105±37 at pH 6.

Preliminary studies show that addition of glycerol to a final concentration of 11.5% preserves peptic activity for at least 60 days when gastric juice is stored at –70°C.

We conclude that pepsin is unstable to usual methods of storage, the rate of decay being inversely correlated with the pH of the sample, and accelerated with freezing. It is possible that reports of changes in pepsin secretion induced by secretagogues may be artefactual because of the altered pH.

F18

Mutagenic activity of gastric juice – further clues to the aetiology of gastric cancer

H J O'CONNOR, S E RILEY, A T R AXON, AND R C GARNER *(Gastroenterology Unit, General Infirmary, Leeds, Microtest Research Ltd., Heslington, York, Cancer Research Unit, University of York, York)*
Mutation tests using modified strains of *Styphimurium* measure the ability of physical or chemical agents to damage DNA and are used to screen substances for potential mutagenicity/carcinogenicity to human beings. Intragastric carcinogens may be important in the aetiology of gastric cancer but the extent of human exposure and their nature remain controversial. To gain further insight in this important clinical area, we have prospectively assessed the mutagenic activity of fasting gastric juice using two strains of *Styphimurium*, TA98 and TA100, in a sensitive fluctuation assay. Gastric juice was aspirated at endoscopy from adult patients with normal endoscopic findings (17), peptic ulcer (62),gastric carcinoma (seven), pernicious anaemia (12), and after surgery for peptic ulcer (22). Ninety three of 121 samples (77%) were found to be mutagenic and 70 of these (58%) were designated as highly mutagenic. Apart from a significant difference in the proportion of highly mutagenic samples detected from patients with gastric ulcer (22/27) compared to normals (8/17) (χ^2, $p<0{\cdot}05$), the proportion of mutagenic samples detected was similar from each of the patient groups studied. A significant increase in mutagenic activity was not detected following therapy with cimetidine or ranitidine in 12 patients. The presence of mutagenic activity was not significantly correlated with hypochlorhydria (pH>4), chronic atrophic gastritis or intestinal metaplasia or with bacterial overgrowth and the presence of nitrate-reducing bacteria in the stomach. Our data suggest that there is widespread human intragastric exposure to potentially genotoxic substances and identification of their nature and source(s) has important implications in the prevention of gastric cancer.

NUTRITION

F19

Patterns of villus cell migration in the small intestine

G WILSON, B PONDER, AND N A WRIGHT *(Department Histopathology, Royal Postgraduate Medical School, London and Institute of Cancer Research, Sutton, Surrey)*
The pathway of epithelial cell migration along the villus has for many years been a topic of conjecture. We describe a model for which the first time clearly demonstrates the pathway taken. The mouse aggregation chimera between a RIII/ro and a C57BL/6 mouse displays a genotypic carbohydrate polymorphism, distinguished by the ability of a cell to bind the plant lectin *Dolichos Biflorus* Agglutinin. In the intestine of such an animal, the crypts will either stain positive or negative to the lectin, the villus staining pattern depending upon the genotype of the crypts feeding it. Using serial tangential sections and plotting the distribution of the labelled/unlabelled cells with a drawing tube and the use of a computer graphics 3D reconstruction facility the pathway has been shown to be in tight cohorts of similar cell type, upwards in straight lines; there is little cell mixing. Also shown is that the villus cell loss may not be confined to villus tips but could also take place from the villus side; the ability of a single crypt to feed cells to more than one villus is also proven. The model allows the migration of cells, as they emerge from the crypt orifices, transverse the vestibule and move onto the villus, to be determined in precise detail, as the crypts supplying the cells can be individually identified. This type of model has undoubted application to other problems in gastrointestinal cell migration.

F20

Effect of carbohydrate, fat and protein on

superior mesenteric artery blood flow in man

M I QAMAR, A E READ, R MOUNTFORD, R SKIDMORE, AND P N T WELLS *(University Department of Medicine, Bristol Royal Infirmary and Department of Medical Physics, Bristol General Hospital, Bristol)* We have previously shown that superior mesenteric artery blood flow (SMABF) measured by transcutaneous Doppler ultrasound technique is increased differentially in response to meals of various caloric content and physical state (liquid or soild). The mechanism of postprandial SMABF increase is still unclear. The present study was designed to investigate separately the SMABF responses to carbohydrate, fat and protein meals.

A set of three experiments was performed in each of 12 healthy volunteers and SMABF was measured before and serially over a period of one hour after three liquid isocaloric meals (each made up to 400 ml and containing 400 Kcal. Meals consisted of carbohydrate (105g caloreen), fat (90 ml prosparol), and protein (110g Maxipro). The SMABF increased within five minutes of the end of each meal (carbohydrate 45% ($p<0.01$), fat 24% ($p<0.1$), and protein 16% ($p<0.05$). The maximal responses were of similar magnitude but reached at different times from the end of the meals: carbohydrate 63% ($p<0.01$) at 15 min., fat 63% ($p<0.01$) at 30 min, and protein 52% ($p<0.01$) at 45 min.

An hour after the end of ingestion, SMABF was still increased: carbohydrate 45% ($p<0.01$), fat 47% ($p<0.01$), and protein 46% ($p<0.01$).

These results show that the chemical nature of the meal is a significant factor determining postprandial SMABE. The mechanism is uncertain but may reflect the differential time course of digestion for the various substrates.

F21

Effects of systemic and luminal adminstration of urogastrone on intestinal epithelial cell proliferation in parenterally fed rats

R A GOODLAD, T J G WILSON, W LENTON, H GREGORY, K G MCCULLAGH, AND N A WRIGHT *(Department of Histopathology, Hammersmith Hospital, London, ICI Alderley Park, Macclesfield, G D Searle, High Wycombe, Bucks)* The location of the main sites of production of the polypeptide urogastone-epidermal growth factor (Uro EGF) in the salivary glands and the Brunner's glands suggests that Uro-EGF may have a role in the maintenance of gastrointestinal homeostasis. Four experiments were performed in which rats were maintained by total parental nutrition (TPN) in order to reduce intestinal epithelial cell proliferation to a basal level and to lessen the effects of luminal nutrition and endogenous secretions.

Ten days of TPN caused a consistent and highly reproducible reduction ($p<0.01$) in intestinal weights and in the rate of accumulation of vincristine arrested metaphases (Crypt Cell Production Rate) ($p<0.001$). Fifteen μg per rat per day of urogastone administered intravenously with an isocaloric amount of the TPN diet significantly increased ($p<0.01 - 0.001$) both the weights of the various sections of the intestine and the CCPR of five sites in the intestine ($p<0.05 - 0.001$). The equivalent daily dose of Uro-EGF administered *via* an intragastric cannulae thrice daily had no significant effect on intestinal weight or CCPR, neither did the luminal administration of higher doses of Uro-EGF (150 and 300 μg/rat/day) have any significant effect on intestinal weight or 2 hour metaphase collection. It is proposed that one of the *in vivo* actions of Uro-EGF is in the maintenance of gastrointestinal growth and that this occurs primarly *via* a systemic mechanism.

F22

Effect of chronic ethanol ingestion on enterocyte turnover in the small intestine

R MAZZANTI AND W J JENKINS *(Department of Medicine, Royal Free Hospital School of Medicine, London)* Whether chronic ethanol ingestion significantly damages the small intestine remains controversial. To elucidate this we have analysed the morphology of the small intestinal epithelium and quantified its renewal in chronically ethanol-fed rats.

Twenty adult male rats were pair-fed for 28 days a liquid diet containing either ethanol at 36% of total calories or an isocaloric diet in which fat substituted for ethanol. Crypt cell production rate (CCPR) was determined in the jejunum and ileum by the metaphase arrrest method.

Weight gain and intestinal morphology were similar in ethanol-fed and control rats, but enterocyte turnover was significantly reduced in the jejunum and ileium of the ethanol-fed rats:

		Ethanol-fed rats	Control rats
Jejunum			
CCPR/h	19·9±1·1	25·6±1·1	$p<0.01$
Crypt/villus ratio	18·4±0·7	21·4±1·8	NS
Net villus influx/h	365±25	548±52	$p<0.05$
Ileum			
CCPR/h	14·2±0·9	21·8±1·0	$p<0.01$
Crypt/villus ration	12·8±0·9	13·0±0·9	NS
Net villus influx/h	181±17	283±23	$p<0.01$

Chronic ethanol ingestion reduces enterocyte turnover in the small intestine. This effect is probably systemic rather than local, because the changes in the jejunum and ileum were similar.

F23

Confirmation of human jejunal Na^+/H^+ exchange and the first demonstration of a congenital defect, using brush border membrane vesicles (BBMV) from jejunal biopsies

I W BOOTH, P J MILLA, G STRANGE, AND H MURER *(Institute of Child Health, London and Physiologisches Institut der Universitat-Zurich, Switzerland)* Although jejunal Na^+/H^+ exchange has been directly shown in the experimental animal using BBMV, the evidence for this important homeostatic mechanism in man is indirect. We have therefore miniaturised the Mg-EGTA precipitation method of isolating jejunal BBMV, using 20–50mg jejunal biopsies obtained from infants and children. A 9x enrichment of alkaline phosphatase occurred during membrane preparation. An Na^+/H^+ exchange mechanism was shown in BBMV, using a rapid filitration technique, by observing a 7x enhancement of sodium uptake at 15 sec, by a pH gradient, (intravesicular pH 6·0; extravesicular pH 7·4) compared with no pH gradient ($p<0.002$). An inward Na^+ gradient (100mM) resulted in a 5x enhancement of D-glucose uptake compared with no gradient ($p<0.05$).

Similar studies were performed in jejunal mucosa from a 3 year old child with secretory diarrhoea which began *in utero*. Steady stat jejunal perfusion studies have shown defective Na^+/H^+ exchange only (1). Studies in BBMV confirmed such a defect, with markedly impaired Na^+ uptake at 15 sec in the presence of an outward H^+ gradient ($p<0.05$) when compared with controls. Na^+ uptake in the absence of an H^+ gradient, and D-glucose uptake were not significantly different from controls.

These data not only provide direct confirmation of the presence of Na^+/H^+ exchange in the human jejunum but also in conjunction with our previous *in vivo* studies describe for the first time, a congenital

defect in this mechanism.

F24

Relationship between intestinal crypt cell production rate and water absorption measured *in vitro* in the perfused rat small intestine

R A GOODLAD, J A PLUMB, AND N A WRIGHT *(Department of Histopathology, Royal Postgraduate Medical School, Hammersmith Hospital, London, and Department of Biochemistry, University of Glasgow, Glasgow)* The measure of the rate of accumulation of vincristine arrested metaphases in microdissected intestinal crypts (crypt cell production rate, CCPR) is the most efficient method of estimating intestinal epithelial cell proliferation which is robust enough to withstand scrutiny. Studies in the field of intestinal adaption, however, could be much more informative if a valid measure of the functional compartment, such as the *in vitro* water absorption capacity could be included. The intraperitoneal injection of 1mg/kg of vincristine, sulphate 30–180 minutes before perfusion, had no significant effect on the water absorption capacity of the small intestine (from the ligament of Treitz to 5 cm before the ileo-caecal valve) as measured by the segmented flow single pass perfusion method. (Control 138·4±4·6, vincristine 144·7±7·8 μl/cm/h).

The CCPR of the jejunum and water absorption of the intestine were then both measured in 25 groups of hypo and hyperproliferative rats which should have been in a 'steady state'. The minimum values were obtained after hypophysectomy (CCPR=6·73±2·87 cells/crypt/h Absorption=68·0±6·67 μl/cm/h) and the maximum values were observed in lactation (CCPR=126·1±20·12 cells/crypt/h Absorption=225·0±16·9 μl/cm/h) The CCPR and absorption were highly significantly correlated ($p<0·001$) when all the data or particular subsets of data were considered, except when a non-steady state model (the intestine of starved rats after refeeding) was investigated. The combined study of CCPR and water absorption is a practical and convenient approach to the study of intestinal cell proliferation and intestinal adaptation, and shows that in 'steady state' models of hypo and hyperplasia cell, production is closely linked to functional capacity.

F25

D-xylose absorption in acute gastroenteritis of known aetiology

M E PENNY, D LLOYD, AND A S MCNEISH *(Institute of Child Health, University of Birmingham and East Birmingham Hospital, Birmingham)* Enteric pathogens infect different and specific parts of the gut – for example, rotavirus (RV) and enteropathogenic *E coli* (EPEC) colonise the proximal small intestine; salmonella and shigella infect the distal bowel. There is a need to devise clinical tests that can follow the course of the intestinal lesion induced by different pathogens.

We have measured the one hour blood xylose (a test of proximal small intestinal mucosal funtion) after intraduodenal infusion of 0·5g/kg D-xylose in a 10% solution in 29 infants with acute diarrhoea aged 0–56 weeks. Longitudinal data were obtained in 15.

Infants with pathogens that damage the proximal intestine had initial blood xylose levels below the lower limit of normal (1·25 mmol/1); RV (n=13) mean xylose 0·97 mmol/1 (range 0·17–2·17); adenovirus (AV, n=2) 0·71, 0·83 mmol/1; EPEC (n=4) 0·53 mmol/1 (0·31–0·71); enterotoxigenic *E coli* (ETEC, n=1) 0·26 mmol/1. All infants with shigella (n=2), salmonella (n=3), no pathogen isolated (n=8), had results within the normal range.

Longitudinal data showed persisting xylose malabsorption during the first week in seven infants with RV, with recovery in the second week (n=4) reflecting clinical improvement. Xylose malabsorption persisted in 1 RV infant with cow's milk intolerance. Three infants with EPEC (two with cow's milk intolerance) had low xylose levels for seven, 24 and 56 days.

This test of xylose absorption discriminated between infants with pathogens damaging different parts of the gut. The test can be used to follow the time course of proximal mucosal damage in gastroenteritis.

F26

Glucose absorption in congenital glucose-galactose malabsorption: a kinetic basis for clinical remission

P J MILLA, E WOZNIAK, AND T R FENTON *(Institute of Child Health, London and Hospital for Sick Children, Great Ormond Street, London)* Glucose-galactose malabsorption (GGM) is an inherited disorder of carrier-mediated intestinal glucose transport. Previous studies have shown failure of microvillous membrane binding but paradoxically clinical amelioration may occur with increasing age.

We have studied the *in vivo* absorption of glucose and fructose in the jejunum of five children (age 1–14 years) with GGM and controls. In eight control subjects glucose absorption obeyed saturation kinetics (appKm 76mmol/l Vmax 25·6μmol/min/cm). In GGM two groups of patients were discernible, GpA(n= 2) with negligible glucose absorption and GpB (n=3) with marked depression of glucose absorption but still by a saturable process (appKm 70 Vmax 3·7). Both groups were significantly different from controls ($p<0·001$) and from each other ($p<0·001$). One patient from GpB over a four year period developed some clinical glucose tolerance. No change was found in affinity for glucose by the transport process, appKm 75 and 80mmol/1; but maximal velocity (Vmax) increased from 4·2 to 10·2 μmol/min/cm.

These data suggest that at least two molecular variants of GGM exist; one where there are no functional transport sites and one where there are decreased numbers of normally functioning transport sites. In this latter group clinical remission may be because of increasing numbers of transport sites.

F27

Two new selective inhibitors of intestinal carbohydrate absorption

R H TAYLOR, HELEN M BARKER, ELIZABETH A BOWEY, AND JEAN E CANFIELD *(Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London)* All dietary carbohydrate except lactose is digested by intestinal α-glycosidases; starch by luminal α-amylase, its products and the disaccharides by brush border α-glycosidases, before absorption as monosaccharides. Two new α-glycosidase inhibitors (BAY m1099 & o1248) have been derived from deoxynojirimycin. Their effects on absorption of six dietary carbohydrates have been compared with those of acarbose using a steady state of perfusion technique.

Young adult female anaesthetised Sprague-Dawley rats had isolated 20cm segments of proximal jejunum perfused *in vivo* at 0·2ml/min for 210 min. Solutions contained 23·4mmol/l of sucrose (n=40), maltose (40), lactose (20), glucose (19) or fructose(15) or 15g l^{-1} starch (36); 3g/1 PEG 4000 labelled with 1μ Ci ^{14}C and NaCl to 290 mosmol. From 60 to 90 min test solutions also contained m1099 6·5mg l, o1248 4·5mg l or acarbose 30mg l or the control solution continued. Each animal had one substrate ± one drug. Sugars were measured by

HPLC, PEG by scintillation counting and disappearance rates calculated in the usual way.

Luminal disappearance rates compared with control fell as follows: sucrose, 51±6% with m1099, 57±7% with o1248 and 68±7% with acarbose (all $p<0.001$); maltose, 50±12% with m1099, ($p<0.001$), 29±10% with o1248 (NS) and 58±10% with acarbose ($p<0.001$); starch, 1±8% with m1099, 7±11% with o1248 (both NS) and 46±9% with acarbose ($p<0.001$). Absorption recovered to control levels in 60–90 min. Disappearance of lactose, a ß-galactoside and the monosaccharides, glucose and fructose, were unaffected by all inhibitors.

We conclude that these new glycosidase inhibitors and acarbose each have different specific and reversible inhibitory characteristics. They provide a valuable way of studying carbohydrate absorption and specific, selective models of intestinal enzyme deficiency.

F28

Plasma PYY is raised after small bowel resection in the rat but does not mediate the trophic response.

A P SAVAGE, G E GORNACZ, T E ADRIAN, R A GOODLAD, N A WRIGHT, AND S R BLOOM *(Royal Postgraduate Medical School, Hammersmith Hospital, London)* Peptide YY (PYY) is a circulating gastrointestinal hormone localised to the endocrine cells of the ileum and colon. The physiological role of PYY is still being defined but it has inhibitory gastrointestinal secretory and motor effects. We have intestigated PYY in the adaptive response following intestinal resection.

Fourteen groups of eight rats underwent either jejunal transection or varying degrees of small bowel resection. Animals were killed at intervals up to 48 days and plasma PYY estimated by radioimmunoassay. Two further groups were given PYY or saline *via* an implanted osmotic pump. Animals were killed at 12 days and plasma PYY, intestinal weight and crypt cell production rate (CCPR) estimated.

Seventy five per cent intestinal resection caused a rise in plasma PYY from a transection value of 28±3 to 85±12 pmol/l ($p<0.001$). This rise was apparent at seven days and maintained to 48 days. Smaller resections showed no significant rise over transection values. Plasma PYY was 141±24 pmol/l in the PYY infused animals compared with 14±4 pmol/l in the saline group. There were no changes in weight of stomach, small bowel, colon and pancreas compared with the control group and no significant changes in CCPR in any region of the gut.

This study shows that PYY is greatly raised after intestinal resection in the rat and while it appears not to exert a major trophic effect, it may mediate other features of the adaptive response.

IBD

F29

Role of sodium cromoglycate in the management of distal colitis

R H GRACE, A E GENT, AND M D HELLIER *(The Royal Hospital, Wolverhampton, Salisbury General Infirmary Princess Margaret Hospital, Swindon, Berks)* After initial enthusiasm, the use of sodium cromoglycate (SGC) in the management of ulcerative colitis has fallen into disrepute. The initial study reported the combined use of oral and rectal administration of SGC but subsequent studies concentrated on the oral route.

In this study, patients presenting with distal disease were randomly allocated blind to prednisone (20 mg) (35 patients) or SCG (600 mg) (35 patients) enema groups; the enemas were used twice daily for 4 weeks and then once daily. Patients were assessed at presentation, and at four and eight weeks. Data relates to symptoms, to appearances on sigmoidoscopy, and to histology.

Each group showed a significant improvement in relation to stool frequency and rectal bleeding both at four and eight weeks, though the Predsol group was more effective at four weeks in relation to rectal bleeding ($p<0.05$). There was, however, no difference in relation to the appearances on sigmoidoscopy and to histology, with both groups again showing significant improvement at four and eight weeks.

It is suggested that there is a place for SCG retention enemas in the management of ulcerative colitis.

F30

Dioctyl sodium sulphosuccinate (DSS), 300 mg daily, does not increase human ileal or colonic output

R W CHAPMAN, J SILLERY, AND D R SAUNDERS *(Department of Gastroenterology, John Radcliffe Hospital, Oxford, and Department of Medicine, University of Washington, Seattle, WA, USA)* Dioctyl sodium sulphosuccinate (DSS) is an anionic detergent which is used widely as a laxative and promoted as a stool softener. Although many anecdotal reports attest to the laxative and stool softening efficacy of DSS, no control trials have been performed to document the effect of DSS on small or large bowel function in man.

We have compared, therefore, the effects of 100 mg DSS three times daily (the maximum recommended dose) with placebo in a randomised, single blind, crossover study in two groups of subjects.

First, six healthy ileostomates were studied while they ate a constant diet for eight days. The daily fibre intake was fixed at either 20 g (four subjects) or 30 g (two subjects). DSS for four days did not increase the daily ileal output of carbohydrate, total fatty acids, bile acids, nitrogen or water, but cholestrol absorption was increased ($p<0.05$).

Second, six healthy volunteers were studied while eating a constant diet of 20 g of fibre plus 30 radio-opaque markers daily so that mean daily transit time (MTT) could be measured. After equilibration, a seven day collection of stool was weighed and lyophilised to measure faecal water. Dioctyl sodium sulphosuccinate had no effect on stool weight, stool frequency, stool water or mean transit time.

We conclude that 300 mg daily of DSS does not increase ileal or colonic output of solids or water in human subjects and may increase cholesterol absorption. The widespread use of DSS deserves reevaluation.

F31

A modified 'gut-sterilisation' regime, compared with oral prednisolone, in a randomised trial for the treatment of Crohn's disease

S H SAVERYMUTTU, H J F HODGSON, AND V S CHADWICK *(Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London)* A randomised clinical trial has been performed, comparing two regimes for the inpatient treatment of active Crohn's disease affecting large or small bowel. Thirty two patients were randomised to receive either: (a) modified 'gut-sterlisation' – an elemental diet (administered by nasogastric tube), plus oral non-absorbable antibiotics (framycetin, colistin and nystatin), or (b) oral prednisolone in a dose of 0.5mg/kg/day, with a

conventional diet. Patients were assessed on admission to the trial and after 10 days treatment, by a clinical index, the Crohn's disease activity index (CDAI), a serological marker (ESR), and by the faecal excretion of ^{111}In over four days after intravenous injection of ^{111}In-labelled autologous leucocytes, and objective assessment of gastrointestinal inflammation. Groups were comparable on admission – 'gut sterilisation' group – CDAI, 222±20 (SEM), ESR – 45±7 mm/h, ^{111}In-excretion 22.5±3% (normal <2%); Oral prednisolone group – CDAI 225±16, ESR 58±16, ESR 58±10mm/h, ^{111}In-excretion 23·9±4%. After 10 days therapy, marked and virtually identical improvement was seen in each group. 'Gut sterlisation' group – CDAI 156±20, ESR 28±6 mm/h, ^{111}In-excretion 10±3%. Oral prednisolone CDAI 136±15, ESR 31±7 mm/h, ^{111}In-excretion 12±3%. The combination of an elemental diet with non-absorbable antibiotics is a rapidly effective treatment, as potent as prednisolone (0·5mg/kg/day) in reducing mucosal inflammation. The mode of action of the 'gut sterilisation' regime is uncertain, but antigen load within the gut lumen, from both dietary and bacterial sources, will have been reduced.

F32

Trials of antimicrobial therapy for relapsing Crohn's disease

N S AMBROSE, D YOUNGS, D W BURDON, R N ALLEN, M R B KEIGHLEY, P BARNES, AND J E LENNARD JONES *(General Hospital, Birmingham, and St. Mark's Hospital, London)* Infection is responsible for many of the complications of Crohn's disease. Furthermore, extra intestinal sites are colonised by pathogenic bacteria in over 50% of patients requiring resection for uncomplicated disease. We decided therefore to undertake a trial of one month's antimicrobial therapy for patients with symptomatic relapse of Crohn's disease.

Criteria for entry included: two major symptoms: fever, abdominal pain, diarrhoea, weight loss, abdominal mass or complications (excluding perianal disease) and two haematological abnormalities: haemoglobin, ESR, CRP, albumen, iron, TIBC. Patients were monitored for the above clinical and haematological parameters over six weeks and for changes in faecal flora. Randomisation was to four groups: Metronidazole alone (M), Cotrimoxazole alone (C), Metronidazole and Cotrimoxazole (C+M) or double placebo (P). Seventy two patients entered the study: 18M, 16C, 21C+M, 17P. After two weeks improvement was reported as follows: M= 67%, C=67%, C+M=71%, P=35%. In the M group two needed an operation and one had side effects, in the C group two developed side effects, in the C+M group four had troublesome side effects and two of the placebo patients required an operation. By four weeks there was no difference in response between the groups (M=44%, C=62%, C+M=57%, P=41%). Antimicrobials had in influence on faecal flora or haematological parameters. These results indicate that antimicrobials appear to have little therapeutic potential for relapse of intestinal Crohn's disease.

F33

Acute effects of glucocorticoids on rectal electrolyte and water transport in normal subjects and patients with ulcerative colitis

G I SANDLE AND H J BINDER *(Departments of Medicine, University of Newcastle upon Tyne, and Yale University, New Haven, Conneticut, USA)* Glucocorticoids are generally assumed to decrease diarrhoea in ulcerative colitis by suppressing mucosal inflammation. Recent studies, however, indicate that glucocorticoids given acutely or chronically, stimulate net sodium (Na) and water (HOH) absorption and potassium (K) secretion in mammalian colon, and may therefore reduce stool volumes in colitic patients, at least in part, by exerting specific effects on colonic transport. To investigate this, a rectal dialysis technique was used to measure transmural potential difference (pd., lumen negative), and net Na, HOH and K movements (+ =absorption; −= secretion) in control subjects and patients with untreated (active) ulcerative colitis, before and five hours after the intravenous administration of glucocorticoid. In controls (n=9), 100 mg of hydrocortisone (HC) increased pd (−36·8±4.9 to −54·1±7.5 mV, p<0·025), and stimulated Na absorption (+3·1±0·6 to +5·4±0·7 mmol.cm^{-2}h, p<0·005). HOH absorption (−3·7±2·9 to +8·8±2·7 ml.cm^{-2}h, p<0·02), and K secretion (−2.0±0·3 to −3·2± 0·6 mmol.cm^{-2}h, p<0·05). Similar changes occurred in controls (n=8) after 40 mg of methylprednisolone. Although pd and transport rates were abnormal in colitic patients (n=6), 100 mg of HC increased pd (−12·0±2·8 to −29·1±7·8 mV, p<0·05), and stimulated Na absorption (+0·4±0·4 to +2·4±0·9 mmol.cm^{-2}h, p<0·025), HOH absorption (−5·8±3·0 to +3·0±2·5 ml.cm^{-2}h, p<0·1). and K secretion (+0·3±0·3 to −0·6±0·5mmol.cm^{-2}h, p<0·05). We conclude that pharmacological doses of glucocorticoids produce similar acute increases in rectal sodium and water absorption in normal subjects and patients with active ulcerative colitis, and this effect may contribute to their ability to decrease diarrhoea in inflammatory bowel disease.

F34

Essential fatty acid composition and prostaglandin E_2 production by peripheral blood cells from patients with Crohn's disease

F J BLOOMFIELD, W J MAXWELL, J P WALSH, F P HOGAN, D KELLEHER, W CLAYTON LOVE, AND P W N KEELING *(Departments of Clinical Medicine and Nutrition and Biochemistry, Trinity College, Dublin, Ireland)* Prostaglandin E_2 (PGE_2) biosynthesis by cultured mononuclear cells from blood or ileal specimens is enhanced in patients with Crohn's disease (CD) compared with that found in control subjects. The aims of this study were to measure the serum and cellular pool of arachidonic acid (AA) and determine if the cellular uptake and conversion of chemical and radiolabelled AA to PGE_2 in peripheral blood mononuclear cells (PBMC) were normal in patients with histologically proven large and/or small bowel CD compared with that found in control subjects (CS).

The results show that PBMC from patients with CD produce greater amounts of PGE_2 compared with that found in CS (n=8, 123±278 *vs* n=8, 45±5 ng/10^6 monocytes, $\bar{x}$±SE, p<0·001, CD *vs* CS) when stimulated with opsonised zymosan (Zy). In the presence of 10 nMoles AA + Zy, the PBMC from patients with CD produced greater amounts of PGE_2 compared with that found in CS (n=6, 1021±286 *vs* n=6, 351±95 ng/10^6 monocytes, p<0·001). Furthermore, the uptake of 10 nmol H^3 AA and conversion to H^3 PGE_2 was of a similar magnitude, (n=9, 1061±242 *vs* n=12, 353±47 ng/10^6 monocytes, p<0·001).

The essential fatty acid AA content of PBMC was significantly higher in patients with CD compared with that found in CS, (n=16, 96±18 *vs* n=12, 48±9 ug/mg DNA, p<0·02). In addition, serum levels showed a similar increase in CD (n=8, 163±25 *vs* n=28, 82±4 μg/ml, p<0·001).

The results of this study show that there is a larger serum and cellular pool of AA in patients with CD. Also, these patients produce significantly greater amounts of PGE_2 when stimulated with opsonised Zy. Our

results would support the concept that PBMC from patients with CD have an enhanced capacity to produce greater amounts of the immunomodulator PGE_2 which might be a consequence of increased availability of precursor AA.

F35

Changes in whole body protein synthesis and breakdown in acute malnourished Crohn's disease patients before and after nutritional restoration

T W O'CALLAGHAN, R DOCKRELL, J R LENNON, M A MORGAN, AND J P CROWE *(Mater Misericordiae Hospital Dublin and Department of Biochemistry and Soil Science, University College Dublin, Eire)* Metabolic changes were studied in seven consecutive malnourished patients with an acute exacerbation of Crohn's disease at the beginning and end of nutrional restoration with a whole protein diet. The nutritional supply provided 2·5 g. of protein and 60 kcal energy/kg/day. Rates of flux, protein synthesis and breakdown were calculated from the enrichment of urinary urea and ammonia with ^{15}N glycine.

Significant nutritional restoration was achieved with mean body weight increasing by 14% from 84% to 96% of ideal, and mean serum albumin by 23% from 35 to 43 g/l ($p<0.02$). Mean rates of whole body protein synthesis and breakdown in the malnourished state were 6·8±1·1 and 5·3±1·4 g/kg/day, respectively. After nutritional restoration these values fell significantly to 4·5±0·8 and 3·3±0·8 g. protein/kg/day ($p<0·02$). These markedly increased rates of synthesis and breakdown show that although whole body protein breakdown is increased in an acute exacerbation of Crohn's disease, this 'catabolic' state is paralled by an equal or greater increase in protein synthesis when the nitrogen and energy supply is adequate. This emphasises the importance of an adequate nutritional supply in the treatment of acute Crohn's disease which in the majority of such patients should be enteral feeding with a whole protein diet.

F36

Diffuse nodular lymphoid hyperplasia and western type malignant lymphoma of the small bowel, without overt immunodeficiency : a signficant association

C MATUCHANSKY, G TOUCHARD, P BABIN, F DEMEOCQ, Y FONCK, M MEYER, AND J L PREUD'HOMME *(Research Group on Digestive Immunopathology, University Hospital, Poitiers, France, University Hospital, Clermont Ferrand, France)* In Mediterranean areas, diffuse small intestinal nodular lymphoid hyperplasia (NLH) may be a histopathologic variant of immunoproliferative small intestinal disease, which is frequently associated with overt malignant lymphoma (ML). In western areas, benign extensive NLH is a well-known entity occurring mainly in immunodeficient subjects. Though very rare, its association with ML is considered to be non-fortuitous; nevertheless, this is based upon only a very limited number of isolated cases observed principally in non-immunodeficient patients. We report the occurrence of small intestinal ML in three out of five consecutive NLH patients without overt immunodeficiency, observed over seven years. Typical benign NLH extending to the whole length of jejunum, ileum and/or duodenum was diagnosed, on operative specimens, in four men and one woman, aged 16 to 32, who presented with long-standing abdominal pain without evidence of malabsorption (four cases), or with intermittent diarrhoea of two year duration (one case). All patients was caucasians: three were born and had lived since birth in central France. Two were born in Portugal and Algeria, respectively, but had lived in France since the age of 2 and 10, respectively. Their socio-economic status was excellent (two cases) or good (three cases). Immunoglobulin levels, systemic antibody response, and delayed hypersensitivity tests were normal. Normal density and distribution of IgA, IgM and IgG-producing plasma cells were found, in each case, in the *lamina propria* both of the small intestine at a distance from the hyperplastic lymphoid nodules, and of the colon and rectum. In the one case studied, the almost exclusive T-cell subset in the germinal centers of the hyperplastic nodules was T8. Intestinal giardiasis was found in two cases. A large ulcerated tumour of the jejunum (two cases) and proximal ileum (one case) was found at laparotomy in three patients (two French and the Portugese), simultaneously to or two years after diagnosis of diffuse NLH. The tumours were B-cell malignant lymphoma of centrocytic-centroblastic type (two patients), and T-cell lymphoblastic lymphoma (1 patient). Tumour resection and combination chemotherapy resulted for two patients in prolonged complete remission. Intestinal NLH persisted unchanged in each case.

We thereby suggest that extensive NLH and ML of the small bowel is a significant association, which may affect caucasians born and living in western countries.

F37

Comparative effects of enteral liquid diets on growth; nitrogen (N) balance, whole body N, N. Wastage and faecal residue in rats.

A N H MAIN, L M NELSON, W EAST, T PRESTON, G MITCHELL, J CUMMINGS, AND R I RUSSELL *(Gastroenterology Unit, Royal Infirmary, Glasgow, Scottish Universities Reactor Research Centre, East Kilbride and MRC Dunn Nutrition Unit, Cambridge)* In a controlled study, five commonly used complete enteral liquid diets differing in nitrogen, carbohydrate and fat composition: Vivonex (V), Vivonex HN (VHN), Flexical (F), Ensure (E), Clinifeed ISO (C), and a control rat chow (Oxoid 41B) were fed to 36 rats (six rats each diet) for 28 days in isocaloric amounts (70.3 Kcal (290KJ) per rat per d.). Mean weight gain (% of starting weight) varied from 35(V) to 58(C), similar to controls (64%), N Balance (mean ±SEM mmol/24h) varied from 7·6±0.5 (V) to 10·7±1·7 (VHN) but no significant differences were observed. Whole body N (neutron activation analysis) (g) after 28d feeding was less with V (8·58±0·16) than F (9·56±1·15) ($p<0·05$) or C (9.39±0.27) ($p<0.05$). Mean N wastage (N excretion as % of intake) was least for F (47) and greatest for E (70), controls excreting 75%. Faecal residue (daily dry weight) was less with V and VHN (230±9 and 180±20mg/d respectively) than F (420±30) ($p<0·01$), E (390±30) ($p<0·01$) and C (570±50) ($p<0·01$). All were <8% of the high residue control diet. Bacterial content of faeces was least for controls (26%) and varied from 46% (VHN) to 65% (C) in the test diets. These differences may reflect the differing digestibility of fibre in the diets.

In conclusion, V produced least growth (N accretion) of the test diets but it and VHN had significantly lower faecal residue than the other test diets. The methods used are applicable to human subjects and the diets will be tested in patients with impaired small bowel function or bowel stricutures in whom low nitrogen wastage and low faecal residue are considered desirable.

F38

Physiological starch malabsorption: direct quantitation in ileostomates and effect of small bowel transit time.

R W CHAPMAN, J SILLERY AND D R SAUNDERS *(Dept of Gastroenterology, John Radcliffe Hospital Oxford and Dept, of Medicine, University of Washington, Seattle, WA, USA)* Recent studies using indirect breath hydrogen and intubation techniques have indicated that in excess of 10% of starch in normal foods may be malabsorbed in the small intestine and enter the colon. The explanation for this phenomenon is unclear.

First, we measured in six healthy ileostomates on a fixed starch intake, 150 g daily for four days, daily unabsorbed dietary starch by chemical analysis of ileostomy effluent. Daily unabsorbed starch ranged from 1·3% to 5·0%, mean 2·4%, of total ingested starch.

Second, we measured in six ileostomates unabsorbed dietary starch from a radiolabelled solid meal containing 50 g potato starch, under control conditions after altering transit time with either loperamide (8 mg) or magnesium citrate (0·1 g/kg body weight). Loperamide significantly prolonged the time taken for the meal to empty from the ileum and significantly decreased the amount of unabsorbed starch in all six ileostomates ($p<0·05$). Magnesium citrate significantly reduced the time taken for the test meal to empty from the ileum and significantly increased starch malabsorption in all six subjects ($p<0·05$). Mean unabsorbed starch (±SD) was 0·8 g± 0·4 after control meal alone; 0·4±0·2 after loperamide and 1·6 g±0·8 after magnesium citrate.

We conclude that the degree of starch malabsorption by the small intestine may be less than previously estimated by less direct methods, and is dependent upon small intestinal transit time.

POSTERS
F39–F133

Regulatory peptides

F39
Polyamine synthesis inhibitor, difluoromethylornithine (DFMO) does not prevent the pancreatic hyperplasia induced by pancreatico-biliary diversion (PBD) in the rat

N H STACE, M HOSOMI, S VAJA, G M MURPHY, AND R H DOWLING *(Gastroenterology Unit, Guy's Hospital and Medical School, London)* Polyamines are thought to regulate cell division and growth: inhibition of polyamine synthesis, therefore, may reduce these processes. Ornithine decarboxylase (ODC) the rate limiting enzyme in polyamine synthesis which converts ornithine to putrescine, is specifically and irreversibly inhibited by DFMO. Thus DFMO in tissue culture reduces cell division and when given orally inhibits adaptive growth in intestine and pancreas – for example, it depresses caerulin induced pancreatic hyperplasia in the rat. To see if DFMO also modifies the pancreatic hyperplasia induced by PBD (interposition of 50 cm of jejunum between stomach and duodenum) eight pairs of rats were given either 2% DFMO in water or drinking water alone beginning two days before PBD.

Both food intake and bw decreased significantly in the DFMO treated rats so that 14 days after PBD, mean bw in the DFMO group (197±SEM 6 g) was less ($p<0·001$) than that in the controls (250±6). As expected, PBD increased pancreatic wet weight by approx 70% in the controls but surprisingly, mean pancreatic weight, corrected/100 g bw, was significantly greater in the DFMO group (847±59 mg) than in the controls (634±26; $p<0·01$). Similarly, mean pancreatic protein (mg 100 g/bw) was also 33% greater after DFMO (138±12) than in the rats given water (103±4; $p<0·02$). Pancreatic DNA (mg 100 g/bw), although greater after DFMO (5·0±0·4) than in controls (4·2±0·3), was not significantly different. Difluoromethylornithine also increased mean testicular weight/100 g bw by 23% ($p<0·001$); it did not significantly affect the weights of heart, kidney, liver, or spleen, when related to bw. When pancreatic and testicular weights were uncorrected for bw, however, there was no difference between the two groups.

These results show that the pancreatic hyperplasia induced by PBD is not inhibited by DFMO. This finding challenges the concept that inhibition of ODC reduces adaptive growth in the pancreas.

F40
Non-equimolor levels of PHI and VIP in the stomach explained by the presence of a big PHI-like molecule

Y YIANGOU, N D CHRISTOFIDES, M A BLANK, N YANAIHARA, A BISHOP, K TATEMOTO, J M POLAK, AND S R BLOOM *(Departments of Medicine and Histochemistry, Royal Postgraduate Medical School, London. Department of Bi-organic Chemistry, Shizouka, Japan, and the Karolinska Institute, Sweden)* Regional specific antibodies and chromatography were used to analyse the distribution and molecular forms of PHI and VIP in the porcine intestine. Concentrations of PHI immunoreactivity (PHI-IR), measured with three different antisera, and VIP immunoreactivity (VIP-IR), were approximately equal in all parts of the gastrointestinal tract apart from the stomach. In the stomach the concentration of PHI-IR, measured with the N-terminally directed antibody (R8403) although equal to the corresponding VIP-IR concentration, was three–four times higher than the PHI-IR concentrations detected with 2 C-terminally directed PHI antisera (T33 and T41). Gel permeation of gastric extracts revealed one VIP-IR peak which co-eluted with the porcine standard at a Kav of 0·5. Only one PHI-IR peak was also detected with T33 and T41. This PHI-IR was eluted in a similar position to the porcine PHI standard (Kav=0·5). With R8403 two PHI-IR peaks were detected, however, the minor form co-eluted with the porcine PHI standard whereas the predominant form eluted earlier (Kav=0·37). The earlier eluting PHI-IR peak was present in the rest of the intestine in only minute amounts. As VIP and PHI are believed to be derived from a common precursor, it is suggested that in the stomach the post-translational enzymic processing of the precursor protein is different from other parts of the intestine, yielding a big PHI-like peptide. As the gastric PHI receptor is known to differ from other tissues, big PHI may have a different biological role. Isolation and pharmacological characterisation of this newly described peptide will undoubtably soon provide an answer.

F41
Localisation and biochemical characterisation of CGRP in brain and gut

M A GHATEI, P K MULDERRY, A E BISHOP, M G ROSENFELD, J M POLAK, AND S R BLOOM *(Departments of Medicine and Immunocytochemistry, Royal Postgraduate Medical School, London)* As a result of alternative RNA processing during calcitonin gene expression an entirely different peptide with 37 amino acid residues called calcitonin gene-related peptide (CGRP) is generated in the rat hypothalamus. As many of the neuropeptides so far described are also located in peripheral tissues, the

distribution of CGRP in the rat gastrointestinal tract, pancreas, and regions of the brain was studied by radioimmunoassay and immunocytochemistry. The highest concentrations of CGRP (pmol/g) were found in the stomach 7·0±1·3, pancreas 5·6±0·8, duodenum 4·4±0·8 and colon 5·0±1·0 with lower concentrations in the jejunum and ileum. In the brain there was considerably more CGRP in the brain stem (37·0±4·8) compared with the other regions. Permeation chromatography of gut extracts revealed three immunoreactive peaks, the major peak co-eluted with synthetic CGRP and two other peaks emerged later. HPLC analysis further resolved one of these into two distinct peaks although most of the CGRP-like immunoreactivity still co-eluted with the synthetic peptide. Immunocytochemistry revealed CGRP-immunoreactivity in an extensive network of nerve fibres in the pancreas and gut. In the pancreas, the fibres were scattered in the exocrine parenchyma and connective tissue and showed a particular association with blood vessels and the islets of langerhans. Calcitonin gene-related peptide fibres were found at the periphery of the islets and also in the midst of the endocrine cells. A proportion of the islet cells were immunostained by the CGRP antibodies. Scattered CGRP-nerves could be seen in the gut. The finding of high concentrations of this novel neuropeptide within the brain and alimentary tract establishes CGRP as another gut-brain peptide and suggests that it may be important in the control of gastrointestinal function.

F42

PYY, a new colonic hormone: changes in gastrointestinal diseases

T E ADRIAN, A P SAVAGE, A J BACARESE-HAMILTON, K D WOLFE, H S BESTERMAN, AND S R BLOOM *(Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London)* Peptide YY (PYY) is a hormonal peptide, recently isolated from porcine intestine, which has been localised to endocrine cells of the ileal and colonic mucosa. Peptide YY potently inhibits gastric secretion in man and also reduces gut motility. Although the abundance of the peptide suggests an important physiological role for PYY in the circulation, its secretion in gastrointestinal diseases has not previously been investigated. Plasma PYY levels, measured basally and after a standard breakfast, were compared in healthy controls and several groups of patients with gastrointestinal disease. Basal PYY concentrations in healthy subjects were 8·5±0·8 pmol/l and showed a small but significant postprandial rise (3·7±0·9, p 0·005). Peptide YY levels were grossly risen in patients with small intestinal mucosal inflammation (sprue, n=9, 79·5±18·0 pmol/l). High basal PYY concentrations were seen in patients with inflammatory bowel disease (Crohn's, n=14, 22·6±3·9, p 0·005; ulcerative colitis, n=24, 13·4±1·5, p 0·01) and in patients with acute infective diarrhoea (n=12, 22·0±4·8, p 0·01); postprandial responses were enhanced in these conditions. In patients with steatorrhoea due to chronic pancreatitis, basal PYY levels were markedly risen (n=12, 49·5±6·3, p 0·001), whereas pancreatic patients without malabsorption had only moderately raised levels (n=21, 15·8±1·5, p 0·001). Peptide YY levels were normal in peptic ulcer and diverticular disease. The rise of plasma PYY levels after food would suggest that this peptide may play an important role as a gastrointestinal hormone. Investigation of the abnormal PYY release seen in gastrointestinal disease may shed light on the role of this interesting hormonal peptide and into the pathophysiology of these common gastrointestinal disorders.

F43

Neural pathways mediating pancreatic polypeptide response to food

C D JOHNSON, J A CHAYVIALLE, M-A DEVAUX, AND H SARLES *(INSERM U31, Marseille, France)* Pancreatic polypeptide (PP) release is mediated by the vagus and is abolished by pyloric transection. We have measured PP release for 45 minutes after food in normal, conscious dogs, with or without atropine 20 μg/kg/h (n=6) and after truncal vagotomy (TV, n=6), coeliac ganglionectomy (CG, n=4) or section of the vagal fibres to the gastric antrum (antral vagotomy, AV, n=4). All operations were performed under general anaesthesia.

Basal PP in controls was 89 pg (eq BPP)/ml (SD:61) and was reduced after AV and TV. The mean PP response (sum of six measurements in each dog) was 3126 (range 1565–4181) in normals. In all other groups the response was reduced (analysis of variance, p<0·001): CG, 2291 (1906–2928), U=4, p=0·057; atropine 1743 (1073–2614) U=3, p=0·015; TV, 489 (130–1246) p=0·001; AV, 440 (158–672) p=0·005.

The effects of atropine and TV confirm previous findings. Coeliac ganglionectomy slightly reduced PP response, consistent with known distribution of some vagal fibres *via* the coeliac plexus. During AV, vagal fibres distal to the pylorus were carefully preserved, but AV abolished PP response. Two possible explanations exist. (1) All efferent fibres to the pancreas might be cut by AV. This seems unlikely on anatomical grounds, and in view of the observed effect of CG. (2) The release of PP after food might be dependent on antro-pancreatic reflexes. Section of the afferent fibres by AV would then abolish the response. The effects of CG suggest that some of the efferents pass through the coeliac ganglion and plexus.

F44

Occurrence and distribution of a novel regulatory peptide, galanin, in the mammalian gastrointestinal tract

A E BISHOP, N D CHRISTOFIDES, J CH'NG, S R BLOOM, AND J M POLAK *(Departments of Histochemistry and Medicine, RPMS, London)* The system of mammalian regulatory peptides continues to expand with the discovery of new active molecules. One of the latest peptides to be isolated and characterised consists of 29 amino acids and has been termed galanin, a name derived from the fact that its N- and C-terminal residues are glycine and alanine Galanin has pharmacological effects on the gut, including contraction of smooth muscle. In this study, immunocytochemistry and radioimmunoassay showed that galanin is present in significant quantities in the gut of mammals, including man. The concentrations of galanin ranged from 2·6 to 77 pmol/g wet weight of tissue and were generally higher in the large bowel. The peptide-immunoreactivity was localised exclusively to a ramifying network of nerve fibres which infiltrated each layer of the bowel wall There was some evidence for a differential distribution of galanin-containing nerves in the various areas of gut. For example, these nerves were numerous in the mucosa of each level of the tract except the stomach, where they were found only infrequently. Neuronal cell bodies containing galanin immunoreactivity were restricted to the submucous plexus mainly of the upper small intestine. Thus, a newly recognised type of peptide-containing nerve has been

discovered in the mammalian gut. The known pharmacological effects of galanin suggest that it is a potential controlling factor but the full extent of its physiological actions and involvement in gut pathology remain to be elucidated.

F45

Monoclonal antibodies to chromogranin A in the demonstration of all currently identifiable endocrine cells of the human gut

A E BISHOP, P FACER, R V LLOYD, B S WILSON, AND J M POLAK *(Department of Histochemistry, RPMS, London, and Department of Pathology, University of Michigan, USA)* A long standing impediment to the visualisation of entire endocrine cell populations has been the lack of reliable, easily reproducible techniques. Previous methods have not always been totally successful. For example, not all endocrine cells are argyrophil and the level of the enzymatic marker neurone specific enolase can vary with cell function, particularly in the lower bowel. Chromogranin A is a protein which has been found in the catecholamine storage granules of adrenal medulla cells. In this study, immunocytochemistry, using monoclonal antibodies to chromogranin A, was applied to test whether the protein can be used as a general marker for all currently identifiable endocrine cells of the gut. Fresh surgical samples of each area of human gut were fixed in formalin and serial sections were cut. The first of each pair of sections was immunostained for chromogranin A and the second for a peptide. In all regions, chromogranin A-immunoreactive cells were more numerous than those showing peptide immunoreactivity. In serial sections, it was possible to see that all types of peptide-immunoreactive cells also contained chromogranin A. The protein was also found in cells which showed no peptide immunoreactivity, suggesting the existence of other endocrine cell types yet to be identified. The density of chromogranin A immunostaining did not vary in the different regions of gut nor in the different cell types. Immunostaining of chromogranin A thus provides a means for the demonstration and rapid assessment of entire populations of gut endocrine cells.

F46

Immunostaining of neurofilaments and neurone specific enolase: a possible means for assessment of the morphological and functional status of the enteric nervous system

A E BISHOP, F CARLEI, P J MARANGOS, J Q TROJANOWSKI, D DAHL, AND J M POLAK *(Department of Histochemistry, RPMS, London, Department of Pathology, University of Pennsylvania, Clinical Psychobiology Branch, NIMH, Maryland and Spinal Cord Injury Research, Boston, Mass, USA)* Neurofilaments and neurone specific enolase (NSE) are both known to be present in the nervous system. Neurofilaments are intermediate-sized proteins of the cytoskeleton whilst NSE is an isomer of a major enzyme of glycolysis. In this study, immunocytochemistry was used to assess and compare the suitability of the two substances as neuronal markers in the enteric nervous system. Fresh specimens of human, porcine, and rodent gut (stomach, small and large intestine) were fixed in formalin or benzoquinone solution and serial 4 μm sections were cut in a cryostat. The first section of each pair was picked up directly from the knife but the second was inverted and picked up. In this way, the same cut face was uppermost in both sections. One section of each pair was immunostained for neurofilaments and the other for NSE, so that a direct comparison could be made of the occurrence of the two proteins in the same neuronal cell bodies. Both proteins could be identified in an extensive network of nerve fibres infiltrating all regions of the gut wall, as well as in the ganglion cells of both plexuses. Neurofilament-immunoreactivity was observed in all cell bodies but some of these were found, in serial sections, to contain no or equivocal NSE-immunoreactivity. This apparent lack of NSE may relate to its level of activity and production in individual cells. Our findings show that immunostaining of neurofilaments allows visualisation of the complete enteric nervous system, irrespective of its functional state, whilst that of NSE may provide information on the dynamic status of the nerves.

Small bowel

F47

Freeze drying technique for faecal fat analysis

T W O'CALLAGHAN, J MCCANN, E WRIGHT, A MORGAN, AND J CROWE *(Mater Misericordiae Hospital, Dublin, University College Dublin, Eire)* To eliminate the traditional lengthy and unpleasant laboratory procedure of homogenisation and heat drying of fresh three day faecal collection for fat analysis, a technique for collection, freeze drying and homogenisation of the total faecal collection in a single container is described.

Freeze drying was performed in a SBFD freeze drying cabinet for 24 hours at 40°C with subsequent homogenisation of the total dry collection in an Atomix homogeniser (MSE) for 15 minutes.

Comparison of results from 25 patients whose faecal fat values range from low normal to grossly abnormal showed highly significant correlation between heat and freeze drying methods ($r=99$, $p<0.01$). Recovery studies using both methods on known fat concentrations (range 0·5 g to 70 g) showed significantly greater accuracy for the freeze drying procedure ($p<0.01$). Reproducibility was tested by multiple analyses (10) at each of seven different known fat concentrations. The coefficient of variance using freeze dry technique was significantly less than for the heat dry technique ($p<0.02$).

Freeze dried faecal analysis has wide applications, and this new technique of dry homogenisation eliminates any need for handling of the fresh faecal collection making it a more acceptable procedure for laboratory personnel. The technique is significantly more accurate and precise than conventional heat drying methods.

F48

Do fibre containing enteral diets have advantages over existing low residue diets?

D H PATIL, G K GRIMBLE, P KEOHANE, H ATTRILL, M LOVE, P G FROST, AND D B A SILK *(Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London)* Fibre modifies the pattern of absorption of the products of luminal starch digestion. The aims of the present study were to determine whether fibre influences the pattern of absorption of protein and carbohydrate after administration of a polymeric enteral diet and to document what effects fibre has on bowel action, stool weight, and gastrointestinal side effects during enteral nutrition.

Six fasted normal volunteers drank on alternate days 750 ml of fibre free polymeric diet (Sokaham; 9gN 1200 Kcal) and the identical diet with 9 g added fibre. The postprandial rises in blood glucose and levels of 17 individual amino acids measured at half hourly intervals for three

hours were similar on both occasions. The addition of fibre was without effect on postprandial breath hydrogen excretion.

In a prospective randomised crossover clinical trial, five patients with normal gastrointestinal function requiring nutritional support were randomised after a five day equilibration period of enteral feeding to receive two five day periods of continuous 24 hour nasogastric infusion of the same polymeric diet (2L; 22 gN, 3200 Kcal) with or without 25 g of fibre. There was no significant difference in daily stool wet weights during infusion of the fibre containing (58±20 g/24h; mean±SEM) or fibre free diet (52±16 g/24h). Bowel frequency (0·8±SE 0·4 *vs* 0·6±0·2 motions per day) was similar during feeding with the fibre containing and fibre free diet and the two diets were tolerated equally well. These findings lend no support to recent suggestions that there could be advantages in using fibre containing diets in enteral nutrition. Low residue diets are less viscous and easier to administer and still appear to be the diets of choice.

F49

The gas enhanced small bowel barium follow through

G M FRASER AND P G PRESTON *(Department of Radiology, Western General Hospital, Edinburgh)* In the radiology of the small bowel the three main criticisms of the barium follow through are (1) that it fails to adequately distend the small bowel lumen and may consequently fail to demonstrate diseased segments, (2) overlapping loops of small bowel may obscure disease and (3) the examination is time consuming.

In order to try to overcome these criticisms each patient is given orally 300 ml of Baritop diluted to 50% W/V and lies on his right side outside the barium room. After approximately half and hour most of the barium will have entered the small bowel. At this stage 100 Baritop effervescent tablets are given in divided doses liberating approximately one litre of gas into the stomach which rapidly passes into the small bowel. Multiple spot films of the small bowel are taken, if necessary with compression. By this method we can significantly increase the amount of contrast medium (barium + air) in the small bowel and at the same time reduce its density thus achieving the twin objectives of distending the small bowel lumen whilst reducing the number of overlapping barium filled small bowel loops.

We have assessed our technique in 58 patients. Although adequate double contrast views of the small bowel were considered to have been achieved in only 25 patients (43%), adequate lumenal distension was achieved in 56 (96%) and adequate separation of small bowel loops in 49 (84%). The examination was completed in under one hour in 25 patients (43%) between one and two hours in 24 (41%) and in over two hours in nine (16%). Each examination took, on average, 25 minutes of the radiologist's time.

These results suggest that the main criticisms of the small bowel barium follow through have been largely overcome by the gas enhanced technique.

F50

Radiometric assay for antigiardial drugs

P M G INGE, A K J GOKA, AND M J G FARTHING *(Department of Gastroenterology, St Bartholomew's Hospital, London)* Antigiardial drug sensitivity testing is not generally available despite evidence of variable parasite susceptibility to standard giardiacidal agents. We describe a 3H-thymidine radiometric method for antigiardial drug assay and relate this to parasite growth during 24 hour culture, and to motility (by phase microscopy) and viability (trypan blue exclusion) both assessed in a four hour microassay. We have investigated antigiardial effects of metronidazole (M) (0·05–400 μM), mepacrine (Mep) (0·05–400 μM) and the bile saltlike antibiotic, sodium fusidate (F) (0·01–1·0 mM) in which we have demonstrated antigiardial activity. Parasite uptake of 3H-thymidine was closely correlated with growth in drug-free control cultures ($r=0·91$, $p<0·001$). Minimal inhibitory concentrations (MIC) for M, Mep, and F were 50 μm, 50 μm and 300 μm respectively at 24 hours for both radiometric assay and growth. At four hours, radiometric assay detected antigiardial activity of F (3H-thymidine uptake ~60% control) but not of M (~100% control). Trophozoite motility at four hours was a less sensitive indicator being reduced to only 50% by drug concentrations in excess of MIC's (M, Mep, and F; >0·2, >0·35 and >0·6 mM respectively) and viability at these concentrations was reduced by only ~20%. Thus the radiometric assay represents a sensitive and objective assessment of antigiardial drug activity and may indicate inhibitory effects of some agents in under 24 hours.

F51

Immunoassay of giardia antigen for diagnosis of giardiasis

A K J GOKA, P M G INGE, AND M J G FARTHING *(Department of Gastroenterology, St Bartholomew's Hospital, London)* Diagnosis of giardiasis relies on the detection of *Giardia* forms in stool (lacks precision) or intestinal aspirate (invasive). We have therefore evaluated the suitability of four immunologic techniques, immunodiffusion (ID), immunoelectrophoresis (IE), countercurrent immunoelectrophoresis (CIE), and indirect enzyme-linked immunosorbent assay (ELISA) for detecting *Giardia* antigen under experimental conditions in stool and intestinal aspirate, Axenic *G lamblia* was used as experimental trophozoite antigen and for antiserum production in rabbits. Cysts were concentrated from stool by a modified Ficoll-Urografin technique. Immunodiffusion, IE, and CIE were performed in 1% agarose in barbitone/barbital buffer, pH 8·6. ELISA was optimised using anti-rabbit Ig linked horse-radish peroxidase as second antibody and tetramethyl benzidine as substrate. Immunodiffusion, IE, and CIE detected experimental Giardia trophozoite antigen but were relatively insensitive requiring a minimum of $8·5\times10^5$ trophozoites for the formation of precipitin lines. These methods failed to reproducibly detect cyst antigen at the concentration tested ($2·3\times10^6$/ml). Enzyme-linked immunosorbent assay, however, detected as few as three trophozoites and 15 cysts and successfully detected Giardia antigen in 12 cyst-positive stools and was negative in 38 of 40 cyst-negative stools. Although preliminary, these studies indicate that stool ELISA for Giardia antigen is a simple and sensitive approach to the diagnosis of giardiasis.

F52

Intestinal permeability changes in asymptomatic travellers to South India

C NOONE, I S MENZIES, AND V I MATHAN *(St Thomas' Hospital, London, and Christian Medical College, Vellore, India)* The urinary excretion ratio of lactulose and L-rhamnose-molecular radii 0·5 and 0·4 mm, may be used to assess intestinal mucosal permeability, both sugars being quantitatively excreted in the urine follow-

ing their unmediated intestinal absorption. Increases in intestinal permeability have previously been shown to be a useful index of mucosal damage.

Eleven visiting medical students who denied any gastrointestinal disturbance were studied one month after their arrival in South India, as were 10 healthy indigenous students in London and South India. Following an overnight fast all subjects ingested an isotonic load containing lactulose 5 g, L-rhamnose 1 g, and collected urine for five hours. Quantitative sugar analysis was carried out by paper and thin layer chromatography.

The visiting students showed an increased lactulose/L-rhamnose excretion ratio (mean 0·12; range 0·01–0·40) compared with both their Indian (0·04; 0·01–0·06) and UK (0·03; 0·01–0·04) non-travelling colleagues. The changes in the excretion ratio were due mainly to increases in lactulose excretion, mean 0·64, 0·24, 0·21% oral load excreted respectively. Two students had sequential studies showing a normal ratio in the UK, increasing (0·1 and 0·3) soon after arrival in India, and returning to normal (0·02 and 0·02) later during their stay. Although symptom-free, increases in permeability were associated with a decrease in whole gut transit time.

Permeability changes of similar magnitude have been described in acute gastroenteritis and during the asymptomatic temporary passage of stool pathogens in infants. The changes described in this study imply asymptomatic mucosal damage, which may be associated with changes in gut flora.

F53

Acetate and bicarbonate enhance cholera toxin induced secretion in the rat proximal small intestine

D D K ROLSTON, M J KELLY, M M BORODO, M J G FARTHING, M L CLARK, AND A M DAWSON *(Department of Gastroenterology, St Bartholomew's Hospital, West Smithfield, London)* Controversy exists as to the ideal composition of oral rehydration solutions. Acetate has been suggested as an alternative to the conventionally used bicarbonate anion in oral rehydration solutions. To study the effect of acetate (5–150 mmol/l) and bicarbonate (30, 50, and 80 mmol/l) on water and sodium transport in the secreting gut we performed steady state perfusions in the rat proximal small intestine. In the normal intestine, maximal water absorption occurred with 80 and 100 mmol/l acetate with mean values of +18·80±3·59 and +25·25±2·78 μl/min/g respectively. Water absorption also occurred from 30, 50, and 80 mmol/l bicarbonate solutions with mean values of +10·17±2·11, +15·15±3·16 and +13·54±2·45 μl/min/g respectively when compared with isotonic saline (+0·88±1·35 μl/min/g, $p<0·01$). Sodium movement paralleled water movement. Surprisingly, after induction of intestinal secretion by cholera toxin, acetate (30 and 100 mmol/l) and bicarbonate (30 mmol/l) both resulted in marked enhancement of the secretory state with mean values of −30·24±4·00, −35·66±5·70 and −28·51±5·90 μl/min/g respectively, compared to isotonic saline (−12·95±2·49 μl/min/g, $p<0·001$). However, 56 mmol/l glucose-saline completely reversed the secretory state to absorption.

In the light of these findings, as well as the results of clinical trials, one must question the use of acetate and bicarbonate in oral rehydration solutions.

F54

Jejunal Na^+ absorption is concentration dependent

B J M JONES, B E HIGGINS, AND D B A SILK *(The Department of Gastroenterology and Nutrition, The Central Middlesex Hospital, London)* Sodium balance may be difficult to attain in patients with short bowel syndrome fed enterally and in whom net Na^+ loss occurs with Na^+ free drinks. The aim of the present study was to determine the critical luminal [Na^+] required for net Na^+ absorption over a short jejunal segment. Thirty three normal subjects underwent steady state perfusion of the proximal 25 cm jejunum with a double lumen-proximal occlusive balloon technique. Twelve different mono-, di-, or polysaccharide substrates of varying osmotic effect but equivalent to 140 mM glucose on complete hydrolysis were perfused at 20 ml/min. Isotonicity was achieved by addition of NaCl (70–152 mmol/l). Na^+ absorption (mmol/h/25 cm±SEM) from 140 mM monosaccharide solutions (5·3±6·2, n=33) was significantly less than from maltose (28·3±2·4, n=6 $p<0·001$) sucrose (25·7±4·2, $p<0·01$ n=6) maltotriose (35·9±3·7, $p<0·001$ n=8), glucose oligomers (38·7±3·1 $p<0·001$ n=10) a complete amylolysate of starch (30·6±4·1, $p<0·001$ n=6). Caloreen (41·3±5·5, $p<0·001$ n=9) and a polysaccharide mixture (28·3±4·8, $p<0·001$ n=8). Na^+ absorption correlated significantly with luminal [Na^+] (r=0·75±0·04, $p<0·0001$ n=112) and perfusate [Na^+] (r=0·62±0·06, $p<0·001$ n=112), but was independent of variations in glucose or water absorption. By extrapolation Na^+ secretion would occur if luminal [Na^+] fell below 74·5 mmol/l or perfusate [Na^+] was <48 mmol/l.

The sodium content of oral sugar-electrolyte solutions or liquid enteral feeds may therefore, be critical for sodium balance in the short gut.

F55

Effects of bacteroides melaninogenicus toxin and bile salts on fat and calcium absorption

K WALSHE, A B J SPEEKENBRINK, C T KEANE, D G WEIR, AND R R O'MOORE *(Departments of Biochemistry, Microbiology and Clinical Medicine, Trinity College and St James' Hospital, Dublin, Eire)* The mechanism for fat malabsorption in the contaminated small bowel syndrome (CSBS) remains controversial. Most authorities consider inadequate micelle formation to be the major factor. Recent studies, however, have suggested a possible role for bacterial toxins in the pathogenesis of CSBS. We have investigated the effects of bile salts and a specific toxin isolated from *Bacteroides melaninogenicus*, a common CSBS isolate, on the functional and structural properties of the isolated loop from rat small intestine.

After exposure of the intestine to the toxin, fat absorption, assessed *in vivo*, was decreased from 604±13 nmol per 10 minutes to 489±23 nmol per 10 minutes ($p<0·005$). Toxin also reduced calcium uptake from 0·907±0·03 nmol/mg/10 minutes to 0·776±0·023 nmol/mg/10 minutes ($p<0·005$) as determined using as *in vitro* tissue slice uptake technique. Deoxycholate (0·25nM) decreased calcium uptake from 0·907±0·032 nmol/mg/10 minutes to 0·761±0·027 nmol/mg/10 minutes ($p<0·005$) but had no effect on fat absorption. Mucosal disaccharidase activity was significantly depressed by toxin and deoxycholate. Electron microscopic findings showed damaged microvilli and mitochondria and swelling of the endoplasmic reticulum. These results suggest that the malabsorption which occurs in CSBS is related to mucosal damage and that bacterial toxins are a possible contributory factor in its causation.

F56
Fasting small intestinal motor activity in chronic idiopathic intestinal pseudo-obstruction (CIIP)

E R WOZNIAK, T R FENTON, AND P J MILLA *(Institute of Child Health, London, and Hospital for Sick Children, Great Ormond Street, London)* Chronic idiopathic intestinal pseudoobstruction usually presents in childhood and may be due to disease of smooth muscle, enteric nerves or alterations of their neuroendocrine environment. We have studied the functional effects of these disease processes using constantly perfused nasojejunal catheters and simultaneously recording motility and myoelectric activity in nine children. In four neonates with a myopathy, migrating motor complex (MMC) like activity was present but both pressure (27·5±8·5 cm H_2O controls 63±19·2 $p<0·02$ mean±ISD) and electrical activity was of low amplitude (3·8±0·8 mV controls 9·65±1·5 $p<0·001$) and not propagated. Three children (7–14 yr) had a peripheral and automatic neuropathy. Amplitude of both pressure (63±19·2 cm H_2O)and electrical activity (9·65±1·5 mV) was normal but abnormalities of propagation with broad ill-formed complexes occurred. In one neonate both a neuropathy and myopathy was present. Migrating motor complex like activity was propagated abnormally and was of low amplitude. In one further child normal cyclical fasting activity was present but the electrical slow wave was of increased frequency (13·5 cpm controls 11·5±0·8). High BP and absent colonic activity suggested increased adrenergic activity which responded well to pharmacological blockade. These studies show that distinct disease processes causing CIIP can be distinguished using manometric and myoelectric recording techniques.

F57
The myenteric reflex: demonstration and significance in man

G P N KENDALL, D G THOMPSON, AND E R WALKER *(Department of Medical Research, St Mark's Hospital, London, and Department of Gastrointestinal Research, The London Hospital, London)* Despite increased experimental and clinical interest in the myenteric plexus, no clinical method exists for testing its integrity. Bayliss and Starling's 'Myenteric reflex' in extrinsically denervated canine jejunum comprised excitation above and inhibition below a zone of distension, and this reflex has been tested in man. Local responses to upper small intestinal distension were recorded in eight healthy, fasted volunteers using a standard perfused tube system. A 5 cm diameter balloon separated three proximal and three distal recording channels. Studies comprised two consecutive three hour randomly ordered periods, during one the balloon was inflated to produce transient discomfort, during the control period the balloon was deflated. Immediately after inflation a marked reduction in total distal motility occurred, over at least 15 cm, which persisted thoughout the study period (mean reduction in contractions = 8·7±0·79 SEM/10 minutes, $p=0·001$)*. Total proximal motor activity showed a small increase (mean increase in contractions = 8·3±3·9 SEM/10 minutes, $p=0·1$).* Normal phase 3 migration, over all six recording channels, occurred in all control studies. During distension duodenal phase 3 contractions commenced normally but never traversed the site of the balloon distension nor did migrating motor complexes start distally over a segment of 25 cm. Phase 2 contractions showed a similar reduction on distal activity (mean reduction in contractions = 5·5±0·94 SEM/10 minutes, $p=0·001$)* and an increase in proximal activity (mean increase in contractions 11·2±4·65 SEM/10 minutes, $p=0·05$)*. Distal motor activity returned rapidly following deflation of the balloon in all but one case. Experiments performed after food produced similar results. This study shows the local response to small intestinal distension in man. The rapidity, localisation and pattern mirrors Bayliss and Starling's observations and is consistent with an intrinsic myenteric response. This reflex may aid evaluation of those clinical motility disorders, where myenteric plexus dysfunction is suspected but for which there is no direct test.

(* Student's *t* test)

F58
Histocompatability antigens and clinical features in coeliac disease

E J ELLIOTT, J A SACHS, J AWAD, C NAVERRETE, AND J A WALKER-SMITH *(Department of Immunology, London Hospital Medical College, and Queen Elizabeth Hospital for Children, London)* The first association of ceoliac disease and an histocompatability antigen was with HLA-BB. Later, a stronger association was made with DR_3 and DR_7. MB_2–DC_3, an allelic specificity of the MB-DC locus which is linked to DR, has recently been shown to have an even stronger association. Thirty per cent of the general population possess this antigen.

The opportunity was taken to look for MB_2–DC_3, in children in whom the diagnosis of gluten intolerance was considered. Three groups of children were studied. Group 1 (n=22) consisted of 15 with proven coeliac disease (ESPGAN criteria); all were positive for MB_2–DC_3: and seven children provisionally diagnosed as coeliac disease by flat mucosal biopsy and response to gluten free diet; all were MB_2–DC_3 positive. Group 2 (n=4) consisted of children with presumed transient gluten intolerance – that is, who are currently gluten tolerant; two were MB_2 – DC_3 negative. In group 3 (n=5) the diagnosis of coeliac disease was excluded; four were MB_2–DC_3 Negative.

The finding has important genetic implications and potential diagnostic value in coeliac disease.

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Gluten in HLA-identical and non-identical siblings of children with coeliac disease

A S PEÑA, MARIA LUISA MEARIN, J LARRAURI, AND ISABEL POLANCO *(Departments of Gastroenterology, University Hospital, Leiden, The Netherlands, and La Paz Hospital, Madrid, Spain)* Genetic and environmental factors are implicated in the pathogenesis of coeliac disease (CD). We have studied the effect of giving 18 g of additional gluten per day in a normal diet during a four week period to healthy siblings (mean age: 10 yr) of coeliac children. Five children were HLA-DR identical, four shared one of the HLA-DR antigens and two had completely different HLA-DR antigens to their respective CD sibling.

Clinical and functional studies consisting of routine blood and xylose tests were performed before, during and after challenge. A jejunal biopsy was obtained at the end of four weeks. Gluten was given in biscuit form (3 g each). Five of these biscuits a day (18 g gluten) produced a clinical and jejunal relapse after four weeks of ingestion – in 12 children who were challenged for diagnostic purposes after two years on gluten free diet. In the healthy siblings no clinical abnormalities were found during the period of the study. In three cases a slight but not significant

decrease in xylose absorption occurred. No histopathological abnormalities were seen in any of the jejunal biopsy specimens at the end of the challenge. The present study does not support the concept that gluten alone is toxic in susceptible individuals who do not have overt coeliac disease. It suggests further that factors other than DR antigens and gluten are also important in disease expression.

F60

Immunoglobulin production during in vitro culture of biopsies from coeliac and IgA deficient patients

G M WOOD, P D HOWDLE, AND M S LOSOWSKY *(Department of Medicine, St James's Hospital, Leeds)* Attempts to study the production of immunoglobulins by the small bowel mucosa have mostly been indirect, with collection of secretions from the small bowel. This method has a number of disadvantages such as contamination by secretions from the biliary system or stomach and degradation of immunoglobulins by digestive enzymes. Such work has indicated that the secretions from untreated coeliac patients have raised levels of IgA and IgM. There is one previous report which describes increased IgA concentration in the culture medium following organ culture of a small bowel biopsy from a single untreated coeliac patient.

We have cultured small bowel biopsies from treated and untreated coeliac and IgA deficient patients and from normal controls and measured IgA, IgG, IgM and IgE concentrations in the culture medium following 24 hours culture.

In 11 untreated coeliac patients, IgM and IgA concentrations were raised compared with 11 normal control patients; IgG was not significantly raised. In 11 treated coeliac patients only IgM remained raised when compared with control patients. There was no additional effect when Frazer's gluten fraction III (1 mg/ml) was present in the medium during culture. IgE was less than 5 IU/ml in the culture medium from all patients. Three IgA deficient patients had markedly decreased concentrations of IgA in the medium and significantly raised IgG and IgM values compared with controls.

These findings show that the untreated coeliac mucosa itself is responsible for the production of increased amounts of IgM and IgA and these changes are reversed by treatment with a gluten free diet. In IgA deficient patients the mucosa produces very little IgA; IgG and IgM increase by way of compensation. The results are compatible with the suggestion that the pathogenesis of the coeliac lesion could be due to antigliadin antibody.

F61

Small bowel mucosal conjugation and pharmacokinetics of ethinyloestradiol in patients with coeliac disease

S F M GRIMMER, D J BACK, ANN COWIE, A ELLIS, I GILMORE, R B MCCONNELL, M L'E ORME, AND J TJIA *(Department of Pharmacology and Therapeutics, University of Liverpool, and Departments of Gastroenterology, Royal Liverpool and Broadgreen Hospitals, Liverpool)* In female patients with coeliac disease there is only minimal impairment of fertility, and the usual method of contraception is the combined oral contraceptive steroid preparation (OCS). The usual oestrogenic component of the OCS is ethinyloestradiol which is extensively conjugated in the small bowel mucosa by conjugation with sulphate. The bioavailability of ethinyloestradiol in normal women is 41·8±9·5% (mean±SE) but this figure might be increased, with toxicological implications, if small bowel disease impaired sulphate conjugation. This study links *in vitro* metabolism data with the pharmacokinetics of ethinyloestradiol in the same patients. Six patients (aged 22–37 years) with confirmed coeliac disease were studied. At diagnostic biopsy, samples of jejunal mucosa were removed and incubated with ^{3}H-ethinyloestradiol. The mean percentage conjugation of ethinyloestradiol was only 5·9±1·7% compared with 16·6±2·9% in eight control women who had histologically normal small bowel mucosa ($p>0·02$). Each patient then received 50 μg ethinyloestradiol by the iv and oral routes on separate occasions and blood samples were collected over a 24 hour period. The bioavailability of ethinyloestradiol was calculated by comparing the area under the plasma ethinyloestradiol concentration versus time curve for the iv and oral doses. The mean bioavailability of ethinyloestradiol was 61·4±12·1% ($n=5$, $p>0·05$) and there was no clear correlation between the *in vitro* gut wall metabolism of ethinyloestradiol and its *in vivo* bioavailability.

F62

Action of cytochalasin B and colchicine on the cytoskeleton of foetal human intestinal epithelium; an in vitro model for congenital microvillus atrophy

R R DOURMASHKIN, L CARRUTHERS, R J SAPSFORD, AND J A WALKER-SMITH *(Laboratory for Paediatric Gastroenterology, St Bartholomew's Hospital, London)* In congenital microvillus atrophy (CMA), there is uptake of brush border material including microvilli into cytoplasmic vacuoles of the gut epithelium. In our laboratory, SDS gel analysis of brush border preparations from a biopsy of this disease showed that myosin, normally present in control biopsies, was greatly diminished. It was suggested that in this condition there is a defect in the actin-myosin function of the cytoskeletal system of the enterocytes that leads to intractable secretory diarrhoea. In this study, we have examined the effect of cytochalasin B (CB), which disrupts microfilaments, and colchicine, which depolymerises microtubules, on enterocytes of human foetal gut epithelium cultured *in vitro*. In this way, we aimed to provide an *in vitro* model for CMA. Electron microscopy of cultures treated with CB showed a biphasic effect. After 40 min treatment, cytoplasmic belbs containing 7 nm filaments (microfilaments) formed at the cell membranes and notably, at the tight junctions of the enterocytes; also, the microfilaments that form the rootlets of the microvilli were either very short or absent. After 24 h treatment, large areas of the brush border were taken up into cytoplasmic vacuoles, and the microvilli within the vacuoles showed various stages of degeneration. SDS gel analysis of brush borders from this preparation showed markedly diminished myosin, as was found in the case of CMA. Colchicine treated cultures showed little uptake of brush border material into the cells, and there was no effect on myosin binding in SDS gel analysis. Control cultures showed neither phenomena. It was concluded that the integrity of the microfilament structure of the cytoskeleton is necessary for the maintenance of the brush border and the actin-myosin system, and that a defect in this system is present in CMA.

F63

Non-invasive investigation of the gastrointestinal tract in collagen-vascular disease

A KESHAVARZIAN, S H SAVERYMUTTU, V S CHADWICK, J P LAVENDER, AND H J F HODGSON *(Royal Postgraduate Medical School, Hammersmith, Hospital, London)* Collagen-vascular diseases frequently affect the gastrointestinal tract, and such involvement is a significant cause of mortality and morbidity. Investigation is frequently difficult in severely ill patients, and yield of conventional investigations such as intestinal biopsy is disappointingly low. We have investigated the use of 111-Indium leucocyte scanning, which would be expected to identify areas of perivascular or generalised neutrophil infiltration, in patients with collagen-vascular diseases suffering from either gastrointestinal symptoms (diarrhoea or abdominal pain, 15 patients) or from otherwise unexplained fever (six patients).

Among patients with gastrointestinal symptoms, seven out of 15 had positive scans suggesting large or small bowel involvement: three out of three patients with Behcet's syndrome, four out of five with vasculitis, but none out of six with systemic lupus erythematosus. Among patients without gastrointestinal symptoms, only one patient (with polyarteritis nodosa) had a positive scan showing both large and small intestinal involvement.

White cell scanning offers a non-invasive, readily tolerated technique for identifying inflammatory involvement of the intestine in patients with collagen-vascular disorders. Involvement of the gastrointestinal tract is rare in the absence of symptoms. Among symptomatic patients, inflammatory involvement of the gut is more likely to be found among patients with vasculitis or Behcet's.

F64
Differing acute phase response in Crohn's disease and ulcerative colitis

S H SAVERYMUTTU, M B PEPYS, V S CHADWICK, AND H J F HODGSON *(Gastroenterology Unit and MRC Acute Phase Protein Research Group, Immunological Medicine Unit, RPMS, Hammersmith Hospital, London)* Crohn's disease and ulcerative colitis are inflammatory conditions of unknown aetiology and unpredictable natural history, but there are no haematological or serological abnormalities which affect their clinical and pathological differences. The most widely used non-specific index of inflammatory activity is the erythrocyte sedimentation rate (ESR) which is raised to a similar extent in both ulcerative colitis and Crohn's disease. It has been suggested that the serum concentration of the acute phase protein, C-reactive protein (CRP) may be higher in Crohn's disease compared with ulcerative colitis for the same degree of inflammatory disease activity, but this conclusion was reached using clinical assessments for judging disease activity. We have now used the technique of faecal ^{111}Indium granulocyte excretion to quantify precisely acute inflammatory activity and performed a prospective correlative study with serum C-reactive protein in 38 patients with Crohn's disease and 30 patients with ulcerative colitis. Patients were divided into groups matched for disease activity according to faecal ^{111}Indium granulocyte excretion. Serum CRP concentration ranged between <2 mg/l – 196 mg/l in Crohn's disease and <2 mg/l – 54 mg/l in ulcerative colitis. For all groups of disease activity serum CRP concentration was significantly higher for Crohn's disease compared with ulcerative colitis ($p<0.01$). No significant difference was found in ESR. These findings show that the acute phase response differs significantly between Crohn's disease and ulcerative colitis. This may reflect a significant difference either in the pathological processes, or in the aetiopathogenesis of these diseases.

F65
Changing scene in Crohn's disease in south-east Scotland

J H ENTRICAN AND W SIRCUS *(Gastrointestinal Unit, Western General Hospital, Edinburgh)* A study of Crohn's disease in south-east Scotland has been carried out, the aim being to determine what changes if any have occurred in the incidence and clinical pattern of Crohn's disease over time. The study is in two parts. An epidemiological study was based on data collected from hospital records of all inpatients treated during the last 20 years in Lothian Region (comprising the City of Edinburgh, Mid-East and West Lothian). The clinical study involved detailed analysis of the case notes of 300 patients with Crohn's disease treated at the Gastrointestinal Unit of the Western General Hospital between 1950 and 1981. The clinical pattern of the disease was compared between two groups divided arbitrarily by year of onset of disease into the two eras 1950–67 and 1968–81.

The results show that overall there has been a three-fold increase in the incidence of Crohn's disease between 1964 and 1979, with a more marked rise in women in recent years. The clinical study discloses that the incidence of toxic megacolon, liver disease arthropathy, and eye disease have shown no significant change with time whereas a significant fall has occurred since 1967 in the occurrence of enterocutaneous and enterovesical fistulae. As regards macroscopic disease, the ileum has become significantly less commonly involved, and the left colon, rectum and perineum significantly more commonly so since 1967.

These data support the view that a change is occurring in the clinical pattern as well as the incidence of Crohn's disease with time.

F66
Intestinal permeability in inflammatory diseases

R T JENKINS, R L GOODACRE, P R ROONEY, R H HUNT, AND J BIENENSTOCK *(Intestinal Disease Research Unit, McMaster University, Hamilton, Ontario, Canada)* Abnormalities in intestinal permeability in inflammatory disease have been recently documented by measuring the urinary excretion of various molecular probes after oral ingestion. The purpose of this study was to elucidate alterations in bowel permeability in patients with Crohn's disease, ulcerative colitis, or rheumatoid arthritis by using an oral dose (ca50uCi) of ^{51}Cr-EDTA, a hydrophilic molecule with a molecular weight of 341·2 dalton. Permeability was assumed to be directly related to urinary excretion of ^{51}Cr-EDTA. A control group of 38 hospital personnel (21 men; 17 women) between the ages of 22 and 56 years and with no overt signs of either inflammatory bowel or joint disease was assembled. A dose of ^{51}Cr-EDTA was administered orally, after an overnight fast, and urine was collected for 24 hours. The normal control group had urinary excretions of the probe molecule from 0·61 to 2·82%/d (mean 1·35%/d; SD, 0·61%/d; median, 1·16%/d; 95% confidence interval, 0·65–2·59%/d). Of the normal controls, no difference could be accounted for upon the basis of age or sex. Nine of 14 patients with active Crohn's disease exhibited increased urinary excretion (range 2·95–7·20%/d) of the probe while all patients in remission had excretion within the 95% confidence interval. Seven of eight patients with active ulcerative colitis had raised excretion (range 4·09–11·23%/d), and seven of eight patients in

remission had normal levels of excretion. Thirteen of 16 patients with active rheumatoid arthritis showed raised excretion (range 2·67–10·2%/d). The differences between the normal control group and the groups with inflammatory diseases were statistically significant (Crohn's disease, $p<0·001$; ulcerative colitis, $p<0·01$; rheumatoid arthritis, $p<0·001$). One patient with acquired immune deficiency syndrome and histologically documented severe atrophy of the intestinal brush border showed a markedly raised urinary excretion (6·38%/d) of ^{51}Cr-EDTA after an oral dose. These findings confirm the work of other groups and provide further evidence that there are disturbances of intestinal permeability associated with inflammatory diseases. The observation that there is increased bowel permeability in patients with rheumatoid arthritis raises the question of a possible intestinal defect that has hitherto not been studied. It seems clear, therefore, that there are increases in gut permeability during episodes of inflammatory diseases, although the mechanism involved in these increases remains unknown.

F67

Can metronidazole and sulphasalazine be used together to treat inflammatory bowel disease?

J L SHAFFER, A KERSHAW, J B HOUSTON, AND L A TURNBERG *(Department of Medicine, Hope Hospital, University of Manchester School of Medicine, Salford, and Department of Pharmacy, University of Manchester, Manchester)* The pharmacokinetics of metronidazole were studied in seven patients with Crohn's disease (CD) and five patients with ulcerative colitis (UC) matched for age, sex, and weight. Multiple plasma samples were assayed for metronidazole after an intravenous dose (400 mg) administered over 20 min and on another occasion after a similar oral dose. Bio-availability was calculated from the two types of concentration/time curves and was found to be 88±0·03% in CD and 92±0·06% in UC. Plasma clearance rates were comparable at 3·24±0·2 l/h in CD and 4·12±0·49 l/h in UC. Elimination half-lives ($T_{\frac{1}{2}}$) were also similar (CD 7·8±0·35 h, UC 6·7±0·64 h). These results are similar to those reported in normal subjects.

The influence of metronidazole on sulphasalazine disposition was determined by measuring plasma sulphapyridine concentrations in the same patients given metronidazole 400 mg b d and sulphasalazine l g b d simultaneously for 10 days. Plasma sulphapyridine concentrations tended to fall in the CD group (day 1, 22·1±2·0 μg/ml; day 10, 15·95±4·5 μg/ml) while it tended to rise in the colitis group (day 1, 26·0±6 μg/ml; day 10, 36·4±8·5 μg/ml). These changes were not statistically different.

Our results suggest that patients with Crohn's disease handle metronidazole in a similar manner to patients with UC and to normal subjects. Metronidazole, unlike other antibiotics, does not appear to interfere with diazo-link splitting of sulphasalazine.

F68

Effect of steroid therapy on ileal zinc metallothionein in Crohn's disease

MARGARET E ELMES, JOHANNA P CLARKSON, B JASANI, AND M WEBB *(Department of Pathology, Welsh National School of Medicine, Cardiff, and MRC Toxicology Unit, Carshalton, Surrey)* Decreased zinc absorption and low plasma zinc are found in poorly nourished patients with Crohn's Disease (CD). Two patients on steroid therapy for CD had an unexpectedly high mucosal zinc measured by radiographic micro-analysis in the ileum. This may be because of steroid induction of synthesis of the zinc binding protein metallothionein (MT). We have recently shown immunoreactivity to MT in formalin fixed human small intestine using antibody to rat liver zinc MT and a sensitive DNP hapten sandwich based immunocytochemical technique. Metallothionein appears to be present in both cytoplasm and nucleus of villous enterocytes, adjacent basement membrane region and lamina propria but was not found in the crypts.

Surgically resected ileal mucosa from five cases CD (no steroids); six cases CD (on steroids) and 12 cases of non-inflammatory bowel disease not on steroids was examined immunocytochemically for MT and scored on a 1–3 subjective scale for intensity and distribution of the resultant staining in three sites; enterocyte cytoplasm; enterocyte nucleus; basement membrane region. Preoperative plasma zinc was measured by atomic absorption spectrophotometry. Results are shown with the overall zinc MT score first and plasma zinc in μ mol/l. Crohn's disease no steroids 2·4 and 10·3; CD on steroids 3·8 and 11·1; non-inflammatory non-steroid controls 3·3 and 11·4. It is clear that both plasma zinc and ileal MT are decreased in Crohn's disease. Steroid administration results in an increase in both indices to the levels observed in the control group which may reflect its therapeutic effect. We conclude that the immunohistological demonstration of ileal mucosal MT provides a new and useful marker of body zinc status in health and disease.

F69

Renal proximal tubular dysfunction in Crohn's disease

P A WINSTANLEY, J B YOUNG, A M BROWNJOHN, E H COOPER, AND A T R AXON *(Renal and Gastroenterology Units, General Infirmary, Leeds, and Unit for Cancer Research, University of Leeds, Leeds)* Alpha-1-microglobulin (α_1M) is a circulating glycoprotein probably synthesised in the liver. It has a low molecular weight (26 000 daltons) and it is therefore filtered by the glomerulus followed by reabsorption and catabolism by the renal proximal tubular cells. Alpha-1-microglobulin is not an acute phase reactant protein and the serum concentration undergoes little change in inflammatory and neoplastic disease. Increased urine concentration is therefore due to increased renal proximal tubular cell function and its measurement provides a sensitive index of the reaction of the kidney to various toxic stimuli.

We have studied the urinary concentrations of α_1M in 22 consecutive patients with Crohn's disease attending an outpatient clinic. The Crohn's disease had been present for one month to 22 years (mean 6½ years) and a Simple Disease Activity Index was 0–15 (mean 9). A random urine sample was collected and urinary α_1M concentration measured by single radial immunodiffusion with the results corrected for urinary creatinine concentration and expressed as mg/g creatinine.

Urine α_1M concentration was increased in 10 patients (>10 mg/g creatinine) (mean (SD) 37·6 (26) mg/g). These findings indicate a previously unrecognised renal proximal tubular dysfunction in Crohn's disease. Its significance is unknown as the patients with raised α_1M could not be distinguished by duration or severity of disease in this small sample.

F70
Evidence of lymphocyte alveolitis in Crohn's disease patients

A CORTOT, B WALLAERT, P BONNIERE, J F COLOMBEL, A B TONNEL, C VOISIN, AND J C PARIS *(Gastroenterology Unit, C.H.R., and Pneumology Department, Hospital A. Calmette, Lille, France)* Reduced lung transfer factor without pulmonary symptoms in Crohn's disease (CD) suggests a latent pulmonary involvement. Bronchoalveolar lavage (BAL) is adequate for detection of alveolar silent abnormalities. Therefore we have assessed pulmonary function tests (PFT) and the cellular characteristics of BAL in 17 consecutive CD: nine women, eight men, 30±7 years (mean±SD) 7 smokers (S), 10 non-smokers (NS) and in 26 controls: nine women, 17 men, 33±7 years, 14 S and 12 NS. None had clinical pulmonary history and all had normal chest radiograph. The CD duration was 53±61 months (1 month to 22 years). The site of CD was small bowel alone (1), colon alone (5), and both (11). Mean CDAI was 196±84 (50 to 355). Seven patients had systemic manifestations: arthritis (four), spondylitis (two), aphtosis (one). Three has sulphasalazine 2 g/day (3 to 36 months). (1) PFT were abnormal in 12 CD, reduced transfer factor being the most frequent (7) (43%). (2) Total BAL cell count and viability of alveolar macrophages were identical in both groups. (3) Alveolar lymphocytes percentages were higher in NS CD:39±24% *versus* 11·5±6% in NS controls ($p<0·0005$) and in S CD 15±14% *versus* 5±3% in S controls ($p<0·002$). 10 CD (59%) had more than 18% of alveolar lymphocytes (normal upper limit: NS and S controls mean +2 SD). (4) There was no correlation between BAL abnormalities and any of CD features or altered PFT. We conclude that lymphocyte alveolitis exists in one of two of our CD patients and is not related to any characteristic of CD and/or pulmonary dysfunction. This suggests a latent pulmonary involvement in CD similar to that described in patients with extrathoracic sarcoidosis or collagen vascular disorders and with normal chest roentgenogram.

F71
Increased metabolism of arachidonic acid in inflamed guinea-pig colon from a model of colitis

N K BOUGHTON-SMITH AND B J R WHITTLE *(Department of Prostaglandin Research, Wellcome Research Laboratories, Beckenham, Kent)* In inflamed colonic tissue from patients with ulcerative colitis, there is an increased synthesis of several prostanoids and also metabolites of the lipoxygenase pathway of arachidonic acid (AA) metabolism, 12-HETE, 15-HETE and LTB_4. These metabolites may have a role in the pathogenesis of inflammatory bowel disease (IBD). We have now investigated the metabolism of AA by inflamed colon from a guinea-pig model of colitis.

Inflamed colonic tissue from guinea-pigs skin sensitised to dinitrochlorobenzene (DNCB, 50 μl, 2·5% in ethanol) and challenged 10 days later with intrarectal DNCB (1 ml; 1% in Orabase) was homogenised and incubated (30 min, 37°C) either alone for studies using RIA for measuring AA metabolites or in the presence of ^{14}C-AA (1·3 μg, 250 nCi). Samples for RIA were frozen directly after incubation. ^{14}C-AA metabolites were extracted and separated with standards by TLC.

Small amounts of PGE_2 6-keto-$PGF_{1\alpha}$ TXB_2 and LTB_4 were formed by guinea-pig colon from endogeneous AA, as measured by RIA. In inflamed tissue the formation of the prostanoids was significantly increased ($p<0·05$); PGE_2 (6·8 × control formation), 6-keto-$PGF_{1\alpha}$ (×2·7) and TXB_2 (×3·8) whereas LTB_4 was unchanged.

The formation of the major ^{14}C-AA metabolites was also significantly increased in inflamed tissue; PGE_2 (10·2 × control), PGD_2 (×3·5), TXB_2, $PGF_{2\alpha}$ and 6-keto-$PG_{1\alpha}$ (all × 2·5). HHT (×5·8) and 11-, 12-, 15-HETE (×2·6).

As in human colon, there is an increase in both prostanoid and HETE formation in inflamed guinea-pig colon, although LTB_4 formation was not increased. The DNCB model of colitis offers an experimental means of investigating the effect of drugs on AA metabolism and the involvement of these metabolites in inflammation.

Colorectal

F72
Excretion and degradation of faecal neutral sterols in human beings under metabolic control

M PONZ DE LEON, P DI DONATO, L RONCUCCI, P REBECCHI, AND N CARULLI *(Clinica Medica I, University of Modena, Policlinico, Modena, Italy)* Evidence has been accumulated, in the last two decades, indicating a relation between diet, intestinal degradation of acidic and neutral sterols by colonic bacteria and the development of colorectal cancer. The issue, however, is still controversial; thus, for instance, the risk of colonic tumours has been associated either to an increased or to a decreased degradation of cholesterol to coprostanol and coprostanone. In normal North Americans on a free diet it has been suggested the existence of two distinct pattern of degradation, one characterised by extensive conversion of cholesterol, the other by little or no conversion. The purpose of this study, therefore, was to evaluate the excretion and the degradation of cholesterol in a large group of volunteers kept under metabolic control.

Thirty eight volunteers (members of the staff or patients without gastrointestinal or other major disorders) were put on a standard solid diet containing a constant amount of cholesterol. Cr_2O_3 (300 mg/day) was given to correct for changes of faecal flow. All faeces were collected for four to six days and each sample separately analysed. Individual sterols were identified and quantified by GLC using 5-cholestane as internal standard.

Daily faecal neutral sterol excretion was 420·4±31·5 mg (mean±SE, range 300–600 mg/day). In all the investigated subjects coprostanol was the most abundant neutral sterol (77·4±2·2%), followed by cholesterol (13·9±1·7% $p<0·001$ versus coprostanol) and by coprostanone (8·9±1·2% $p<0·001$ versus coprostanol, $p<0·02$ versus cholesterol). Epicoprostanol and cholestanone were detected only in a few patients and in trace amounts. Percent of degradation (coprostanol + coprostanone) ranged between 63 and 98%.

This study suggests the existence of only one major pattern of cholesterol conversion in the normal human intestine – that is, cholesterol is largely degradated to its metabolites by colonic bacteria. In our opinion, previous reports of two degradation patterns depended on external influences (diets, alcohol and other beverages) due to the lack of metabolic control.

F73
Inhibitory effect of peppermint and menthol on human isolated coli

B A TAYLOR, D K LUSCOMBE, AND H L DUTHIE

(Department of Surgery, Welsh National School of Medicine, Cardiff, and Division of Pharmacology, Welsh School of Pharmacy, Cardiff) Peppermint oil (PO), which improves some symptoms of irritable bowel syndrome, exerts its inhibitory effect on guinea-pig ileum *via* a mechanism involving calcium antagonism. We have now investigated the effects of PO and of menthol, the major component of PO, on human isolated taenia coli. A total of 50 strips of taenia, approximately 30×3 mm, were dissected from 20 resections for carcinoma. Tissues were either used immediately, or stored overnight at 4°C in Kreb's solution (mM: NaCl 118·0; KCl 4·7; $CaCl_2$ 2·5; $MgCl_2$ 1·2; $NaHCO_3$ 25·0; NaH_2PO_4 1·4; glucose 11·5). Unless otherwise stated, experiments were carried out after 30 minutes equilibration at 37°C in Kreb's solution bubbled with 5% CO_2 in O_2. No gross differences were observed in stimulated responses or in spontaneous activity in tissue taken from different regions of the colon. Peppermint oil and menthol produced both inhibition of spontaneous activity and decrease in basal tone in all tissues in a dose-dependent manner. Under isotonic conditions (tension 2 g), ID_{50} values (concentration of antagonist producing 50% reduction in response to carbachol, 10^{-6}M) were calculated for menthol (0·29±0·11 mM; n=5) and for PO (0·41±0·06 mM; n=5: estimated MW 160). Under isometric conditions, dose-response curves to carbachol (10^{-7}–10^{-4}M) and to potassium (5–150 mM) demonstrated non-competitive inhibition by both PO and menthol, this effect being rapidly reversible on wash-out. In calcium-free, depolarising Kreb's solution (mM: NaCl 82·7; KCl 40·0; $NaHCO_3$ 25·0; NaH_2PO_4 1·4; glucose 11·5), dose-response curves to calcium (0·1–20 mM) showed a specific calcium antagonist effect of menthol, which was dose-related and rapidly reversible. These results indicate that the inhibitory effect of PO on human taenia appears also to involve calcium antagonism, and that menthol is mainly responsible for this effect.

F74
Abnormalities of rectal distensibility in the irritable bowel syndrome

J S VARMA AND A N SMITH *(University Department of Surgery/Urology, Gastro-Intestinal Wolfson Laboratory, Western General Hospital, Edinburgh)* There is indirect evidence of increased intestinal tone in patients with the irritable bowel syndrome (IBS) leading to spasm and oversensitivity to distension. We have measured rectal sensation, volume and distensibility in IBS patients with constipation and compared it with an age and sex-matched asymptomatic control group of subjects (n=10). A proctometrogram was obtained by inflating a highly compliant rectal balloon at a constant rate (67 ml H_2O/min) and monitoring intraluminal pressure by a microtransducer. Volumes (V ml H_2O) were recorded at threshold and constant sensation and maximal tolerance (MTV). Pressures (Pcm H_2O) were recorded simultaneously and rectal compliance (RC, ($\Delta V/\Delta P$) ml/cm H_2O) was calculated on the linear portion of the graph. Seven out of 10 patients in the IBS group complained of extreme 'pain' and urgency compared with 'discomfort' in the control group at the MTV. The induced pain was of the same quality and site as their presenting complaint. There is a significant reduction in volumes at the constant sensation and MTV in the IBS group compared with controls (volume at constant sensation, mean 154±26 SEM v/s 290±23, $p<0·01$; MTV 294±32 v/s 505±25. $p<0·01$) but not in volume at threshold sensation (mean 122±17 SEM v/s 210±30, $p>0·05$; Wilcoxon's signed rank sum test). Rectal compliance was also significantly reduced (IBS mean 3·8±0·5 SEM v/s controls 8·5±0·5, $p<0·01$). A correlation exists between MTV and RC ($r=0·9$, $p<0·01$). Comparable pressure measurements showed no significant differences.

This study indicates increase of rectal tone in the constipated IBS group which may be responsible for the reduced volume tolerance and oversensitivity to distension.

F75
Tissue oxygen tension and Xe^{133} clearance in the assessment of intestinal perfusion and the effect of vasodilators

A SHANDALL, R LOWNDES, H L YOUNG, E O CRAWLEY, AND K G LEACH (INTRODUCED BY J V PSAILA) *(Departments of Surgery and Medical Physics & Bioengineering, University Hospital of Wales, Cardiff)* No reliable methods of assessment of intestinal tissue perfusion are available. We have studied Doppler ultrasound, laser Doppler and oxygen tension compared with Xe^{133} clearance in devascularised intestine. The methods used were: (1) 10 MHZ Doppler and spectral analyser. (2) Laser Doppler Velocimeter. (3) Xe^{133} clearance with scintillation counter. (4) Clark-type oxygen electrode and a picoammeter. Twenty segments of rabbit intestine were variably devascularised from terminal mesenteric vessels to main mesenteric artery, with later revascularisation. Doppler ultrasound measured velocity in the mesenteric vessel, but not tissue flow. Laser Doppler was sensitive to movement and the readings were not reproducible. The oxygen electrode has proved easy to use, and was reproducible. The electrode was calibrated in air and O_2 depleted solutions, the temperature coefficient was 4% per °C. The relation between O_2 tension and Xe^{133} clearance has shown that the intestine is able to adapt to reduced blood flow until a critical level of 30% is reached (Xe^{133} clearance $t_{\frac{1}{2}}$ 280 (s). The use of vasodilators was then assessed using isoprenaline, naftidrofuryl, isoxsurpine, and a thromboxane synthetase inhibitor. The first three vasodilators reduced blood flow and oxygen tension to the colon as perfusion pressure was reduced to lowering of systemic blood pressure. The thromboxane synthetase inhibitor did not effect blood pressure and increased oxygen tension. It is concluded that the use of the O_2 electrode in assessing intestinal viability shoud be studied. The effect of the thromboxane synthetase inhibitor on intestinal ischaemia and anastomoses warrants further investigation.

F76
Granulocyte migration to uncomplicated intestinal anastomoses in man

A KESHAVARZIAN, R GIBSON, J SPENCER, J P LAVENDER, AND H J F HODGSON *(Royal Postgraduate Medical School, Hammersmith Hospital, London)* Experimental work shows that neutrophil leucocytes are not necessary for process of wound repair in skin in animals, although they accumulate in aspetic wound within the first two days. The histological sequence of events in intestinal anastomoses is the same as those seen in wound healing elsewhere in the body, but, owing to presence of bacterial flora, the magnitude, duration and implications of neutrophil migration might be different. We therefore investigated this, using 111-Indium granulocyte scanning in patients with uncomplicated intestinal anastomoses. Eight patients underwent resection and anastomosis (right hemicolectomy five, sigmoid colectomy two, ileal resection one). All

patients had an uneventful postoperative course, with no evidence of any leakage or infection. 111-Indium granulocyte scan and abdominal ultrasound were performed 7–20 days (12±4·7, x̄±SD) following surgery. ^{111}In scan showed the presence of labelled granulocytes at the site of anastomosis in all patients. In three out of eight, cells subsequently passed into the lumen of the bowel. In contrast, granulocytes were not visualised along the abdominal incision. In all cases, abdominal ultrasound was normal with no evidence of abscess or collection. Thus, in contrast to skin wounds, granulocytes continue migrating into the intestinal wall in areas of anastomoses for up to 20 days. The role of granulocytes in intestinal repair may therefore be different from elsewhere in the body. Moreover, this phenomenon has an important clinical implication, as ^{111}In granulocyte scanning is now being used following intestinal surgery for detection of infection and inflammation. The normal appearances seen in uncomplicated intestinal anastomoses should not be confused with abscess or diffuse mucosal inflammation.

F77

Sacral evoked response – a useful index of neuropathy in faecal incontinence

J S VARMA AND A N SMITH *(University Department of Surgery/Urology, Gastro-Intestinal Wolfson Laboratory, Western General Hospital, Edinburgh)* Stimulation of the dorsal nerve of the penis or clitoris evokes a response at the bulbocavenous and external anal sphincter muscles which is dependent on an intact reflex arc mediated *via* the sacral spinal cord. To assess its usefulness in the detection of neuropathy we have measured the latency of the anal sphincter response in 14 women patients with idiopathic faecal incontinence and 22 asymptomatic control subjects using an averaging electrophysiological technique.

Submaximal train stimuli (duration 0·1 msec, frequency 2 Hz, voltage approximately three to four times sensation threshold) were applied by a surface electrode. One hundred to 200 anal sphincter responses were detected by a surface bipolar platinum anal plug electrode and the digitally average response recorded (sweep 100 msec). The procedure was repeated for each subject.

Stable and constant responses were obtained in all cases. The control group showed a latency range of 27·2–47·6 msec (mean 37·7±1·4 SEM). All incontinent patients showed abnormalities; four had absent responses and 10 showed prolonged latencies (range 49–66·4 msec; mean 56·4±1·8 SEM). This prolongation is significant when compared with the control group ($p<0·01$, Wilcoxon's rank sum test) and is not age-dependent.

This study indicates that the latency of the sacral evoked response is a useful index of neuropathy. The abnormal responses demonstrated in idiopathic faecal incontinence in this disorder suggest a neurogenic aetiology. Electrophysiological recording of the evoked response by the technique is a convenient and reliable method of assessing the innervation of the pelvic floor.

F78

Open access flexible sigmoidoscopy – a useful contribution to the management of patients with lower gastrointestinal symptoms?

A M ROE, K D VELLACOTT, AND N J McC MORTENSEN *(University Department of Surgery, Bristol Royal Infirmary, Bristol)* As up to 25% of patients with colorectal cancer are still admitted as emergencies we have investigated the place of an open access flexible sigmoidoscopy service (FS) in the management and early diagnosis of patients with rectal bleeding or symptoms suggesting colorectal disease.

Of the first 150 consecutive patients, 89 presented with rectal bleeding, 59 with change in bowel habit and 24 with abdominal pain. Thirty one per cent (46) had a normal examination, but 13% (20) had a colorectal neoplasm, 16% (24) diverticular disease, 9% (13) proctitis or colitis and 24% (36) had haemorrhoids.

A full examination was achieved in 76% and only 5% had insufficient bowel preparation. Of those with diverticular disease (DD), 83% had a limited examination to <50 cm ($p<0·001$ compared with non-DD), as a result of narrowing (13), pain (five) or failed preparation (two).

Twelve adenomatous polyps were found in 11 patients. Carcinoma was found in nine (five rectal, four sigmoid): two Dukes' B and six Dukes' C. A barium enema was arranged in 17 patients (11%), significantly more in those with DD than normals ($p<0·05$). One polyp missed by FS was discovered by subsequent barium enema.

These results suggest open access FS will yield a reasonable proportion of positive findings including neoplasms, but there was no evidence that carcinoma was found at an earlier stage. Elderly patients with diverticular disease may first need a barium enema, but FS may save unnecessary examinations in others. Flexible sigmoidoscopy has a place in the prompt investigation of lower gastrointestinal symptoms.

F79

Epidermal growth factor binding in normal and cancerous human gut epithelia

ALLISON F WREN, S R CROSBY, AND J B ELDER *(Department of Surgery, Manchester University Medical School, Manchester)* Virus-transformed cells and certain human tumour cells produce transforming growth factors (TGF's). Transforming growth factor-I is structurally related to EGF and competes with it for the EGF receptor on cell membranes. We have measured the binding of ^{125}I-EGF to the cell membranes of human gastric and colonic adenocarcinomata, to non-cancerous but adjacent 'normal' epithelia and to the cell membranes of one truly normal colon. Aliquots of the crude membrane fractions containing 100 μg protein were incubated with varying concentrations of ^{125}I-EGF. Bound and free peptide were separated by filtration. From Scatchard analysis of the binding data we have shown that carcinomas of the ascending colon bound 0·017 pM EGF/mg protein, significantly less ($p<0·05$) than adjacent 'normal' membranes (n=4, 0·03 pM/mg protein). Similarly, carcinomatous tissue of the sigmoid bound less EGF (0·11 pM/mg protein) than normal membranes (0·29 pM/mg protein). This spectrum of EGF binding – lower in ascending and transverse colon than in sigmoid – was also apparent in the truly normal colonic membranes. Antral carcinoma bound less EGF than their adjoining 'normal' mucosa, though this difference was not significant. These results are consistent with the proposal that gut carcinomas produce a species of TGF-I which can utilise the normal EGF receptor to mediate its role in the growth of neoplastic cells, thereby reducing the amount of exogenous EGF that can be bound to the membranes.

F80

Faecal carcinoembryonic antigen (CEA) in patients with colorectal cancer

R S STUBBS, BAIRD I MCLEAN, AND J E SHIVELY *(Hillingdon and West Middlesex Hospitals, Middlesex, and City of Hope National*

Medical Center, Duarte, California, USA) The early promise of serum CEA measurement for detecting colorectal cancer has regrettably not been fulfilled because of inadequate sensitivity and specificity. Immunofluorescent techniques have localised CEA primarily to the cell membrane of tumour cells. It may therefore be that colorectal cancers shed CEA into the bowel lumen. This is indeed the case. We measured faecal CEA in 21 colon cancer patients and 24 controls by a radioimmunoassay technique utilising a conventional polyclonal antibody. As measured by this system CEA was present in large amounts in all subjects. Paradoxically, the concentrations were somewhat higher in the controls than in the cancer patients (mean±SE 44·6±14·3 μg/g *vs* 18·7±4·9 μg/g; p=NS). In a subsequent study faecal CEA was measured in seven colon cancer patients and seven controls utilising a monoclonal antibody in an enzyme linked immunoassay. Carcinoembryonic antigen values in the controls ranged from 0 to 1·7 μg/g and those in the cancer patients from 0·4 to 27·0 μg/g, with only one patient having a concentration of less than 2·0 μg/g. Mean±SE for the two groups were 0·74±0·22 and 10·76±3·65 μg/g respectively ($p<0·05$).

Further work may show faecal CEA to be a valuable diagnostic and perhaps screening test for colorectal cancer. In this context an assay using a monoclonal antibody appears to offer greater specificity than one utilising a conventional polyclonal antibody.

F81

Use of a questionnaire and four tumour markers to identify cancer risk in a symptomatic population

E M CHISHOLM, R MARSHALL, D BROWN, E H COOPER, AND G R GILES *(University Department of Surgery, St James's Hospital, Leeds, and Unit for Cancer Research, University of Leeds, Leeds)* There is currently much debate as to the role of multivariate analysis and scoring systems, applied to symptoms, to identify high risk individuals for significant gastrointestinal disease. A similar approach to predict the probability of GI cancer, using a panel of tumour markers, has successfully identified 81% cancers, with a false positive rate of 16%. We have combined these two approaches to determine whether the addition of tumour markers to symptom analysis has any merit.

Eighty six subjects with gastrointestinal cancer, 168 subjects with proven benign GI disease and 750 individuals attending their practitioners with non-gastrointestinal complaints were assessed. Each person completed a 41 item questionnaire and gave a blood sample for the estimation of CEA, C-reactive protein, alpha-l-acid glycoprotein and gamma glutamyl transpeptidase.

To establish a series of probability coefficients an initial logistic regression analysis was applied to 54 cancer patients, 80 benign cases, and 200 GP subjects, and using these coefficients, the remaining cases were assessed. In the initial analyses, permitting only a 5% false positive rate, the questionnaire identified 60% cancers, the tumour markers 67% cancers, and the combination 92% cancers (χ^2 $p<0·05$). Applying the probability coefficients prospectively to the remaining cases, 88% cancers were detected with a false positive rate of 11%.

Although a scoring index for symptoms is simple to use, on its own there is a considerable risk of missing significant disease. The addition of the tumour markers to the system however does indicate a reasonable number of subjects at 'risk' of bearing a cancer.

F82

Immunological and haemoccult detection of faecal occult blood in patients with colorectal carcinomas and polyps

D J FROMMER AND A KAPPARIS (INTRODUCED BY S SHERLOCK) *(Departments of Medicine and Gastroenterology, St Vincent's Hospital, Sidney, NSW, Australia)* Immunological methods of detecting faecal occult blood have a higher specificity and sensitivity than chemical ones. This study investigated the ability of Haemoccult II kits (with faecal samples tested with and without preliminary rehydration) to detect bleeding from colorectal carcinomas and polyps, compared with a radial immunodiffusion method with a detection limit of 2 mg haemoglobin/100 g faeces. Testing six faecal samples from patients with carcinoma with the immunological method, Haemoccult II, with and without rehydration, gave 180/234 (76·9%), 153/234 (65·4%) and 120/228 (52·6%) positive samples representing 39/39 (100%), 34/39 (87·2%) and 28/38 (73·7%) patients with at least one sample positive. Each method gave an appreciably lower proportion of positive samples from patients detected by screening compared to those detected by clinical symptoms and also a lower proportion of positive screened patients with both Haemoccult methods. Patients with colorectal polyps had 141/432 (32·6%), 100/402 (24·9%) and 44/402 (10·9%) positive samples with the three methods. Patients with polyps diagnosed through screening had a higher proportion of samples and patients positive with each method compared to those diagnosed as part of a routine follow up study.

We conclude (1) bleeding from colorectal carcinomas and polyps is detected more frequently by an immunodiffusion technique than by using Haemoccult II kits, whether rehydration is used or not. (2) The data suggest that 100% of colorectal carcinomas have detectable bleeding using the immunodiffusion technique with six samples. (3) The frequency of positive samples and patients will be influenced by the way in which patients have been selected, as well as the technique used.

F83

Faecal occult blood screening in symptomatic patients in general practice

N C ARMITAGE, P A FARRANDS, K D VELLACOTT, AND J D HARDCASTLE *(Department of Surgery, University Hospital, Nottingham)* Colorectal cancers tend to present late, with many months delay between the onset of symptoms and diagnosis. A controlled trial of faecal occult blood testing in patients attending their family doctor with gastrointestinal symptoms was instituted to attempt to reduce the time from consultation to diagnosis. Patients over 45 with abdominal symptoms were designated to test or control group. The former were given three-day faecal occult blood testing and the latter were identified and managed in the conventional way. Those test subjects with positive tests were investigated by flexible sigmoidoscopy and double contrast barium enema.

Two hundred and ninety nine patients (181 test, 118 control) were entered into the study. In the test group 180 (99%) completed the tests and there were 33 (18%) with positive tests. Five colorectal cancers and one oesophageal cancer (mean delay before seeking medical advice 8·7±8·6 weeks) have been diagnosed with a mean time to diagnosis from consultation of 16·5±9·6 days. Six colonic adenomas have been diagnosed with a mean time to

diagnosis of 22·6±10·2 days. In the control group five patients with colorectal cancer and one patient with carcinomatosis (primary unknown) have presented (mean delay 12·6±14·0 weeks) with a mean time to diagnosis of 105±114 days. Two patients have presented with adenomas with a mean time to diagnosis of 62·5 days.

The time to diagnosis for cancers and adenomas is significantly shorter in the test group (overall U = 4·5, p<0·001, cancers U = 5, p<0·002). Faecal occult blood testing of patients attending their family doctor with abdominal symptoms is well accepted and significantly reduces the time to diagnosis of colorectal tumours.

Biliary

F84

Mono-octonoin therapy – combined experience in 343 cases of retained biliary calculi

K R PALMER AND A F HOFMANN *(University of California, San Diego, CA, USA)* The gall stone dissolution agent mono-octonoin (MO) has only been available from a single centre on a named patient basis. Between January 1980 and September 1983, complete records of MO therapy were available on 343 gall stone patients, (this includes several who have been the subject of smaller reports).

Age ranged from 17–93, mean 65·5 years. Two hundred and twenty six patients were women. Two hundred and fifty presented with biliary calculi more than six months after biliary tract surgery, 55 had retained calculi after recent surgery, 38 had a gall bladder *in situ*. Two to ten millilitres an hour (mean 5·9) of MO was constantly infused *via* T tube (230 cases), nasobiliary catheter (82), PTC (23) or cholecystostomy (eight). In 88 patients (26%) calculi disappeared. In 70 (21%) stones became smaller but remained. In 29 (9%) it was thought that MO contributed to successful endoscopic therapy. One hundred and twenty four patients (33%) failed to respond and side effects curtailed treatment in 32 (9%) patients. Mean dissolution time was 10 days (SD 3), and successful therapy was unrelated to stone size or number. Side effects occurred in 67% of cases; the commonest were abdominal pain (36%), nausea (28%), cholangitis (8%) and diarrhoea (15%). Life threatening complications including septicaemia (four cases), gastrointestinal haemorrhage (three cases) and pulmonary oedema (one case) were rare.

Mono-octonoin therapy is moderately effective though side effects are common.

F85

Ursocholic acid (UCA): a new potential agent for dissolving cholesterol gall stones

P LORIA, G MEDICI, R IORI, AND N CARULLI (INTRODUCED BY M PONZ DE LEON) *Istituto di Clinica Medica I, Università di Modena, Modena, Italy)* We have recently reported that lipid secretion into bile is inversely related to the hydrophilicity of the bile acid (BA) pool. Ursocholic acid the 7β-hydroxyepimer of cholic acid (CA) is more hydrophilic than ursodeoxycholic acid (UDCA). Its effect on biliary lipid secretion has not yet been reported in man. The aim of the present study was to evaluate the effect of acute intraduodenal infusion and short term oral administration of UCA on biliary lipid secretion and BA composition.

Acute infusion: three T-tube patients were infused with UCA in conditions of interrupted enterohepatic circulation. The infusions were performed at a rate of 1 g/h for five hours, after five hours depletion of the endogenous BA pool. The same procedure was employed for five infusions with UDCA. Oral administration: 10 gall stone patients were administered UCA at a dose of approximately 15 mg/g/die for 2 weeks. Bile acid composition and biliary lipids were evaluated on bile samples before and after acute infusion and oral administration.

The results show that after acute infusion UCA reached by 2h 85–95% of the BA pool and it induced a significantly lower cholesterol (CH) and phospholipid (PL) secretion than UDCA. Slope values of the regression lines for CH/BA secretion were 0·03 for UDCA and 0·01 for UCA, those for PL/BA were respectively 0·12 and 0·04. Oral administration: after treatment UCA constituted 20·5±8·68% of the BA pool, deoxycholic increased from 30·35±19·7 to 42·55±18·33 (p<0·01) while chenodeoxycholic and CA decreased. Mean saturation index (SI) fell from 1·22±0·22 to 0·99±0·17 (p<0·05) but in four patients in whom basal SI was less than 1 there was no significant variation respect to pretreatment value.

We conclude that after acute replacement UCA, which is more hydrophilic than UDCA, induced a lower lipid secretion. This effect may explain its desaturation properties at only one fourth substitution of the BA pool and raises the possibility of its use in gall stone dissolution therapy.

F86

Deoxycholic acid (DCA) feeding induces signficant changes of biliary lipid composition in cirrhotic patients

F CARUBBI, M PONZ DE LEON, P DI DONATO, AND N CARULLI *(Istituto di Clinica Medica I, Università di Modena, Modena, Italy)* Feeding of bile acids such as chenodeoxycholic acid or ursodeoxycholic acid to humans is associated with a selective expansion of the fed bile acid pool and a sharp decrease of biliary cholesterol saturation. It has also been shown, by some authors, that DCA feeding increases bile cholesterol saturation, especially in small doses close to the daily intestinal DCA production. As DCA is the most detergent among the physiological bile acids it has been suggested that the capacity of different bile acids to stimulate cholesterol secretion into bile could be relevant to biliary lipid secretion and saturation. To test this hypothesis we investigated the effect of small doses of DCA feeding on bile lipid composition in cirrhotic patients, characterised by a very small DCA pool. Eleven patients with advanced liver cirrhosis were hospitalised and put on a standard diet providing 400 mg cholesterol/day. Fasting duodenal bile samples were obtained by intubation after cerulein induced gall bladder contraction; bile samples were collected the first time one week after beginning diet, the second time after three weeks on DCA (3 mg/kg/day per os) and the third upon discontinuing DCA ingestion, four weeks later. Bile lipids were measured with standard techniques and biliary bile acids by gas liquid chromatography.

Biliary bile acids pool composition changed significantly during DCA feeding: the fraction of DCA in bile rose sharply from a mean pretreatment value of 5·36±4·9% to a post-treatment value of 43·9±12% (p<0·001, Student's paired *t* test) and returned to basal values after discontinuing treatment (5·9±4·7%). As expected, the increase of DCA was associated with a marked reduction of the fraction of the other bile acids. Bile cholesterol saturation index (calculated according Carey's critical tables) rose from mean values of 0·92±0·26 before DCA feeding to 1·34±0·47 after DCA ingestion (p<0·005) and returned to 0·91±0·44 after

discontinuing DCA feeding. No hepatic alterations or other side effects were observed during DCA treatment.

We conclude that in a selected group of patients with very small biliary DCA, treatment with low doses of this bile acid led to marked changes of bile acid pool composition in the sense that when DCA pool expansion was obtained by DCA feeding, bile cholesterol saturation significantly increased. These findings lend further support to the hypothesis that modifications of the detergent power of biliary bile acids pool induced by DCA feeding influence bile cholesterol secretion and saturation.

F87

Gall stone pathogenesis: evidence of separate nucleation and equilibrium solubility effects after addition of calcium salts to biliary lipid systems

B W A WILLIAMSON, M TRAINER, AND I W PERCY-ROBB *(University Departments of Surgery, Royal Infirmary and Pathological Biochemistry, Western Infirmary, Glasgow)* The rate of growth of crystalline cholesterol in purified bile-salt-lecithin-cholesterol-water systems was studied over 60 minutes in the presence of crystals of calcium carbonate in three size ranges: 5–10 μm, 100–300 μm, and >300 μm. Overall growth was inversely proportional to the calcium crystal size: 1·45, 0·70, and 0·46 mg/ml/min respectively reflecting the different total surface areas of the three crystal groups. The cholesterol growth rate per unit area was, however, higher for the larger crystals than for the smaller crystals (0·340 and 0·035 mg/ml/min/cm^2 respectively). Similar experiments were performed with calcium carbonate, hydroxyapatite, calcium bilirubinate, and cholesterol microcrystals. In these experiments also, cholesterol growth occurred within the first 60 minutes. These studies were extended for 21 days. Cholesterol growth continued in the presence of hydroxyapatite or cholesterol crystals down to saturation indices (CSI's) of 0·60–0·70. By contrast in the presence of calcium carbonate and calcium bilirubinate, growth ceased at CSI's >0·90. Scanning electron microscopy at the end of all these experiments showed cholesterol crystals both directly attached to the seed crystal and also free in the suspension. These data lead to the conclusion that crystals of compounds that occur in gall stones influence the solubility of cholesterol in biliary lipid systems by at least two different mechanisms; (a) nucleation onto the seed crystals; (b) alteration of the equilibrium solubility of cholesterol. The relative importance of these effects depends on the chemical nature of the seed crystal and on the time available for growth to occur.

F88

Biliary calcium secretion in man has bile acid-dependent and acid-independent components

D GLEESON, N SCRIVENS, G M MURPHY, AND R H DOWLING *(Gastroenterology Unit, Guy's Hospital and Medical School, London)* Although 10–30% of gall stones in developed societies contain calcium and are radio-opaque, little is know about factors influencing biliary calcium secretion in man. Therefore, in five T-tube patients studied seven to 10 days postcholecystectomy, we examined the relationships between bile flow, bile acid (BA) and biliary calcium concentrations, first with an intact entero-hepatic circulation (after clamping the T-tube for 48–60 h) and then in 30 min collections of T-tube bile for five to eight hours, as bile flow and BA concentrations fell during depletion of the BA pool by washout.

As planned, the BA concentrations in the T-tube bile fell progressively with time from maxima of 9–56 mM to 2–7 mM during the washout. There was a corresponding fall in bile flow and in all five patients, we confirmed significant linear correlations between bile volume and BA output ($r=0·60–0·96$; $p<0·05–0·001$) thereby validating the model. In four of the five patients, biliary calcium concentrations [CA^{++}] also fell during BA pool depletion by 50–60% from maxima of 1·80–3·25 mM and there were positive correlations between biliary [CA^{++}] and BA concentrations, which were highly significant in three ($r=0·80$, 0·84, and 0·96; $p<0·005$). By extrapolation, there were positive intercepts with the ordinate so that at zero BA concentration, the BA independent fraction of bile flow still contained 0·83–1·1 mM calcium.

We conclude that: (i) in man, as in animals, biliary calcium secretion seems linearly related to BA output. (ii) As for bile volume, there are BA-dependent and BA-independent components of biliary calcium secretion, and (iii) in most patients, the BA-dependent component of bile flow is richer in calcium than the BA-independent component.

F89

Short-term biliary stenting in the management of sclerosing cholangitis

I HAMILTON, J S SOUTAR, A CUSCHIERI, AND I A D BOUCHIER *(Departments of Medicine, Surgery and Radiology, Ninewells Hospital and Medical School, Dundee, Scotland)* The value of dilatation of the biliary tract with long term biliary stenting in the management of sclerosing cholangitis has been shown. We describe three patients in whom a short period of biliary stenting produced effective relief of extrahepatic stricture with no effect on intrahepatic disease.

All had inflammatory bowel disease with sclerosing cholangitis diagnosed by cholangiography and liver biopsy preoperatively. Colectomy and exploration of the biliary tract were performed and a silastic stent with multiple side holes passed through the liver and into the duodenum. Stents remained *in situ* for 3–11 months. All patients have undergone ERCP after removal of the stents. In each case, radiological, and biochemical criteria suggest considerable improvement in extrahepatic disease occurs shortly after insertion whilst intrahepatic disease may improve only after longer periods of stenting.

We believe short term biliary stenting may be valuable in the management of extrahepatic sclerosing cholangitis but a prolonged period may be necessary to effect intrahepatic disease.

Pancreas

F90

Effects of somatostatin on experimentally induced pancreatitis in the rat

J N BAXTER, S A JENKINS, C R MACKIE, N ROBERTS, D W DAY, W H TAYLOR, AND R SHIELDS *(Departments of Surgery, Pathology and Chemical Pathology, Royal Liverpool Hospital, Liverpool)* Although it has been suggested that somatostatin (SRIF) may be of value in the treatment of acute pancreatitis, there is little evidence to support this claim. Therefore, we studied the effects of SRIF on experimentally induced pancreatitis in the rat.

Pancreatitis was induced in 20 male Wistar rats by ligating the common bile

duct at its point of entry into the duodenum. Twelve hours later, 10 rats received a bolus dose of 4 μg SRIF followed by a constant infusion of 4 μg/kg body wt/h for 24 hours. The remaining rats received a bolus dose and an infusion of the same volume of saline. All rats were bled before and after the induction of pancreatitis and again 12 hours after the start of the SRIF or saline infusion.

After the induction of pancreatitis there were increases in serum amylase and serum lipase, ($p<0.01$, Students t test) in all rats. Twelve hours after the start of SRIF infusion, nine of the 10 rats were alive and the serum amylase (4538 ± 225 to 1619 ± 72.3 U/L) and serum lipase (3.06 ± 0.46 to 1.1 ± 0.1 U/L) were significantly reduced. In the group of rats receiving saline only five rats were surviving after 12 hours of infusion and the serum amylase and serum lipase had significantly increased. Only two rats receiving SRIF died in the 24 hour period after the induction of pancreatitis whereas all rats receiving saline died.

These results suggest that SRIF may be of value in the treatment of acute pancreatitis.

F91

Pulmonary sequestration of radiolabelled autologous platelets in acute pancreatitis in the rat

I A GOULBOURNE, H WATSON, AND G C DAVIES (INTRODUCED BY R C HEADING) *(Departments of Clinical Surgery and Haematology, Royal Infirmary of Edinburgh, Edinburgh)* The pathogenesis of the severe respiratory complications of acute pancreatitis remains unclear, but probably involves leukocytes, fibrinogen/fibrin conversion and complement activation. We have reported increased intrapulmonary fibrin deposition in pancreatitis and correlated this with increased lung wet weight and decreased compliance. In the present series of experiments, 2 ml of blood were withdrawn from specific pathogen free adult male Sprague Dawley rats for labelling with Indium 111 oxine. The rats were partially rehydrated and pancreatitis induced. Rats received the labelled platelets (100 kBeq) and one 125 fibrinogen (20 kBeq) intravenously at the end of the operation. The rats were killed at 18 hours, the lungs were removed and scinticounted for fibrin and platelet deposition.

Pancreatitis was confirmed by raised concentrations of amylase in the pancreatitis group.

Platelet entrapment was significantly higher in pancreatitis animals ($p<0.001$). These significance values held true when the percentage radioisotope uptake was corrected for body mass.

Increased platelet deposition has been confirmed in lungs of animals with acute pancreatitis and may contribute by way of the platelet release reaction to the pulmonary complications of this disease in man.

F92

Lecithin is important in maintaining pancreatic duct integrity

C P ARMSTRONG, T V TAYLOR, AND H B TORRANCE *(Department of Surgical Gastroenterology, Manchester Royal Infirmary, Manchester)* The pancreatic duct possesses a barrier (PMB) to free back diffusion which is damaged by the natural detergents, bile salt and lysolecithin. Although lecithin may have a physiological role in the protection of biliary and intestinal epithelium, its effects on the pancreatic duct is unknown.

The bile-pancreatic duct of rats was perfused at low pressure at 100 μl/h with a standard solution (SPS) [Na^+ 150, HCO_3^- 120, Cl^- 30 mmol/l] – period I, with the test solution – period II and with SPS again – period III. The difference in ionic flux (μmol/cm/h) of Cl^- (ΔJCl) and HCO_3^- ($\Delta JHCO_3$) and transductal potential difference (ΔpD, mV) between periods III and I was calculated. Damage to the PMB was indicated by a change in the pD with electron microscopic (EM) confirmation. The test solutions were (A) SPS (control), (B) 10 mM glycodeoxycholate (GDC), (C) GDC + 50 mM lecithin, (D) lysolecithin, (E) lysolecithin + 50mM lecithin ($n=10$ for each). SPS alone (A) did not affect duct integrity. Both bile salt (B) and lysolecithin (D) produced significant changes in ion flux and pD and EM showed epithelial disruption. The addition of lecithin (C,E) significantly reduced the increased permeability produced by both detergents. (Glycodeoxycholate; reduction in ΔJCl, $\Delta JHCO_3$, and ΔpD; each $p<0.01$, Mann-Whitney U test; lysolecithin also reduction in ΔJCl, $\Delta JHCO_3$ and ΔpD; each $p\mu 0.01$). Ultrastructural examination revealed that lecithin had prevented any epithelial damage.

Lecithin in the bile may be an important moderator of pancreatic duct damage induced by the natural detergents, bile salt and lysolecithin. A reduced biliary concentration of lecithin renders the bile more noxious

F93

Low circulating androgens and high oestrogens in pancreatic adenocarcinoma: evidence for a possible hypothalamo-pituitary defect

T P CORBISHLEY, J J KEATING, M J IQBAL, M L WILKINSON, P J JOHNSON, AND ROGER WILLIAMS *(The Liver Unit, King's College Hospital and School of Medicine & Dentistry, London)* The previous observation that pancreatic tumour tissue contained oestrogen and progesterone receptors and increased aromatase and 5α-reductase activity has led us to investigate the pattern of total and free plasma sex steroid hormone concentrations and the integrity of the hypothalamo-pituitary axis in patients with pancreatic carcinoma. The total and free plasma concentrations of testosterone (T), 5α-dihydrotestosterone (DHT), 17 oestradiol (E_2) were measured in 47 pancreatic tumour patients (28 men), 45 tumour control patients (27 men), and 40 age and sex matched healthy controls. The free plasma E_2 concentrations were significantly raised in male pancreatic carcinoma patients (median 35 pmol/l (range 10–86)) compared with the tumour controls (median 7 pmol/l (range 3–31)) and healthy controls (median 19 pmol/l (range 10·7–30)) ($p<0.001$). The free plasma T was significantly lower in men with pancreatic carcinoma (median free T 46 pmol/l (range 6–1447)), and tumour controls (median free T 29 pmol/l (range 4–1089)), than healthy controls (median free T 826 pmol/l (range 290–1600)), ($p<0.001$) but no difference existed between the tumour groups. Basal plasma LH and FSH concentrations, measured in 19 patients with pancreatic tumours were within the low normal range. LHRH stimulation showed a normal FSH response but a reduced LH response however. The high plasma E_2 concentrations seen in patients with pancreatic carcinoma are consistent with increased aromatisation of androgens by tumour tissue. The results also indicate that the reduced concentration of plasma androgens may result from a defect in the hypothalamo-pituitary axis.

F94
Liver histology in non-jaundice patients with pancreatitis: a clue to aetiology?

H H ALI, N Y HABOUBI, AND J M BRAGANZA *(Pathology Departments of Withington Hospital and the Medical School, Manchester, and University Department of Gastroenterology, Manchester Royal Infirmary, Manchester)* Thirty three consecutive non-jaundiced patients had a liver biopsy between 10 days and 6 months after an attack or relapse of pancreatitis (acute eight, chronic 25): five additional patients had painless chronic pancreatitis. Possible aetological factors were alcohol (eight), a drug (five), type IV hyperlipidaemia (two), and gall stones (two): pancreatitis was 'idiopathic' in the remainder (55%).

Altered hepatocytes, occupying 10–100% of the parenchyma, were detected in 23 of the 38 cases (60%). Their appearances varied from large pale cells with 'clear' cytoplasm to typical ground-glass hepatocytes: toluidine blue staining of ultra-thin sections revealed extensive microvesicular fat in three biopsies. Some biopsies showed excess lipofuscin or steatosis. The portal tracts were altered in 28 cases (74%): the changes included diffuse lymphocytic infiltration, focal bile duct proliferation, focal ductopenia and features suggestive of primary biliary cirrhosis or sclerosing cholangitis. The spectrum of hepatocytic and/or portal tract abnormalities was similar in patients with acute pancreatitis and chronic pancreatitis.

Ground-glass hepatocytes are associated with microsomal 'induction' by drugs; microvesicular fat with damage by reactive intermediates, and lipofuscin with lipid peroxidation within tissues. Our findings thus collectively suggest that the hepatobiliary changes that accompany pancreatitis may represent hepatic induction by xenobiotics, and the consequence of 'oxidative detoxification'.

Liver

F95
Ontogeny of iron absorption and its possible relationship to pathogenesis of haemochromatosis

S K S SRAI, E S DEBNAM, M BOSS, AND O ESPTEIN *(Department of Medicine, Royal Free Hospital School of Medicine, London, and Department of Physiology, Department of Medical Physics, Royal Free Hospital, London)* Haemochromatosis is caused by a defect in the control of iron absorption from birth. In this study we have investigated the possibility that haemochromatosis is caused by persistence of the neonatal mode of iron absorption. As it is not possible to study the ontogeny of iron absorption in the human, we have studied the developing guinea pig.

Whole body iron absorption in developing guinea pigs ranging in age from <24 hours to adulthood was measured by administering an oral dose of ^{59}Fe. Mean serum iron in the neonatal and adult guinea pig was 74 μM (70–84) and 49 μM (32–70) respectively. Iron absorption at birth ranged between 40–60% of the dose. By 10 days iron absorption decreased to the adult range (<10%). This development process was further investigated by studying mucosal uptake and total iron absorption, using isolated duodenal loops perfused *in situ* with varying concentrations of iron (10 μM–2000μM) complexed with nitrilotriacetic acid and labelled with ^{59}Fe. Chromium (^{51}Cr) EDTA was used as an unabsorbable marker to correct for non-specific uptake. At all concentrations studied, both duodenal mucosal iron uptake and total absorption was significantly increased in the neonate compared with the adult ($p<0.002$). The increase in mucosal iron uptake in the neonate and the rapid change to the adult mode in the postnatal period indicates a fundamental alteration in the physiology of iron absorption. Inappropriate iron absorption in the neonatal guinea pig is similar to the abnormalities in haemochromatosis. Persistence of the neonatal mode might underlie the increased iron absorption occurring from birth in haemochromatosis. Study of factors controlling neonatal iron absorption might provide new insight into the pathogenesis of haemochromatosis.

F96
"In vivo" evaluation of cholesterol 7α-hydroxylation in liver cirrhosis

M BERTOLOTTI, D MENOZZI, F ZIRONI, AND N CARULLI (INTRODUCED BY M PONZ DE LEON) *(Istituto di Clinical Medica I, Università di Modena, Italy)* It has been shown that qualitative and quantitative alterations of sterol metabolism are associated with liver cirrhosis. Particularly, a reduction of bile acid pool size has been described, mainly because of the elective reduction of cholic acid synthesis. The mechanisms responsible for these changes have not been well defined.

The aim of this study was to investigate the first committed and rate-limiting step of bile acid synthesis, that is the 7α-hydroxylation of cholesterol, in patients with cirrhosis.

Subjects investigated included five normal controls and seven patients with different degrees of severity of liver disease. The severity of the disease was graded by means of a scoring systems. Each subject received about 200 μCi of 7α-^{3}H cholesterol dissolved in 20 ml of plasma. Blood samples were taken at fixed intervals for four to five days, for the assay of specific activity of plasma free and esterified cholesterol. Samples of blood cells were lyophilised to obtain the sublimate for radioactivity assay of body water. Volume of body water was estimated by dilution of a small amount of tritiated water given 15 days after the study was completed. From the specific activity-time curves of both plasma cholesterol and body water the amount of cholesterol undergoing 7α-hydroxylation at any given time interval could be calculated from the equation: increase of specific activity of body water/specific activity of cholesterol.

The results show that 7α-hydroxylation of cholesterol was significantly ($p<0.01$) decreased in patients with cirrhosis (116±82 mg/24 h) compared with normal controls (314±108 mg/24 h). The values of 7α-hydroxylation were inversely correlated ($r=-0.94$; $p<0.001$) with the severity of the disease.

Our data show that patients with liver cirrhosis have an impairment of cholesterol 7α-hydroxylation, which seems to parallel the extent of liver involvement. These findings suggest that the factor responsible for the decreased bile acid synthesis is the reduction of liver cell mass.

F97
Plasmapheresis in fulminant hepatitis

J G FREEMAN, K MATTHEWSON, AND C O RECORD *(Department of Gastroenterology, Royal Victoria Infirmary, Newcastle upon Tyne)* Fulminant hepatitis (FH) carries a high mortality regardless of its cause. Recent research has been directed towards charcoal haemoperfusion, which is only effective in 20% of cases when treatment is started after the patients has been unresponsive to commands (Grade 4 coma). Plasmapheresis is a simpler

technique with few side effects, allowing removal of 'hepatic toxins', and providing essential plasma nutrients to support the patient during hepatic regeneration. Our experience of plasmapheresis in cases of FH is reported.

Patients were eligible for the study if they had FH and were in grade 4 hepatic coma. Nine patients with FH underwent a 3 litre exchange using a Haematech plasmapheresis machine, the discarded plasma being replaced by equal quantities of fresh frozen plasma, and plasma protein fraction. No significant side effects were encountered. The mean number of plasmaphereses performed on each subject was three.

Five of the nine patients made a full recovery, and the remaining four died as a direct consequence of hepatic failure. In the preceding three years and during the study period, 11 patients with FH and grade 4 coma did not undergo plasmapheresis, and only two patients survived.

Thus, the survival rate in our plasmapheresed series was 55% compared with a survival of 18% in the non-plasmapheresed patients ($p=0.027$, Fischer's exact test). The results are encouraging, and further studies indicated.

F98

Hepatocyte plasma membrane lipid fluidity – a regulator of membrane transport?

P R MILLS, P J MEIER, J L BOYER, AND E R GORDON *(Gastroenterology Unit, Royal Infirmary, Glasgow, and Liver Study Unit, Yale University School of Medicine, New Haven, USA)* The fluidity of plasma membrane lipids may influence membrane protein-related functions such as transport. In this study we examined the effect of ethanol on this relationship. Basolateral plasma membrane vesicles (right-side-out) were prepared from rat liver. Membrane fluidity (anisotropy, r) was measured by fluorescence polarisation using diphenylhexatriene as a lipid probe. Uptake of ^{3}H-taurocholate was measured by a rapid Millipore filtration technique.

Baseline anisotropy of basolateral vesicles was 0.2262 ± 0.0040 (mean±SEM, $n=8$). Ethanol produced an instant concentration-dependent fluidising effect ($p<0.01$) from 50 mM ($\Delta r=-12.6\pm3\times10^{-4}$) to 500 mM ($\Delta r=-103.6\pm11\times10^{-4}$). Taurocholate uptake into basolateral vesicles (a Na-coupled carrier-mediated process) was inhibited in parallel to changes in membrane fluidity (correlation = 0·98).

These studies show that ethanol produces a dose-related effect on liver plasma membrane fluidity and simultaneously inhibits taurocholate transport. These findings suggest that the fluidity of the hydrophobic region of plasma membrane lipids is a regulator of membrane transport.

F99

Microtubules and the control of vesicle traffic in hepatocytes

R COLEMAN, S G BARNWELL, AND P J LOWE (INTRODUCED BY E ELIAS) *(Department of Biochemistry, University of Birmingham, Birmingham)* Protein secretion from hepatocytes occurs both from the sinusoidal pole of the cell (plasma proteins carried in secretory vesicles originating from the endoplasmic reticulum-golgi) and from the canalicular pole (secretory IgA, and secretory component, carried in vesicles originating from the sinusoidal plasma membrane).

Colchicine (and other microtubule disrupting agents – for example, vinblastine) reduce the secretion of plasma proteins from hepatocytes into blood. Colchicine also reduces the output of secretory IgA into bile from bile-fistula rats and form isolated perfused livers.

In contrast, the bile from these colchicine treated animals contains greater amounts of plasma albumin than corresponding controls. If colchicine is added to the perfusion fluid of a liver perfused with rat plasma protein-free medium it promotes the secretion of rat plasma albumin into bile.

This phenomenon is not restricted to albumin, however, as bile from colchicine-treated livers also contains fibrinogen, transferrin etc; these proteins cannot be detected in untreated livers. Colchicine treatment does not, however, result in gross cell damage under these conditions, because there is no loss of cytosol proteins.

By electron microscopy the livers of colchicine treated animals contain an abundance of small vesicles, many of which are located close to the bile canaliculus. It is therefore suggested that: (i) vesicles normally destined for secretory processes at the sinusoidal pole of the cell can discharge their contents into bile when the microtubular system is disrupted, (ii) it is the microtubular system rather than vesicle-membrane recognition which may determine the normal direction of traffic through the cell.

F100

Validation of a new chromogenic assay for endotoxaemia in liver disease

E M ALSTEAD, F J KHAN, A I MORRIS, I T GILMORE, AND J WARE *(Department of Medicine, University of Liverpool, Liverpool)* The measurement of endotoxaemia in liver disease has been difficult, unreliable and, at best, only semiquantitative. With the development of a kit using a new chromogenic substrate and limulus lysate (Byk Mallinckrodt), we have validated its use in patients with liver disease. Standard curves using crystalloids appeared linear, with a mean gradient of 0.88 ± 0.083 SD. Using normal plasma to which known amounts of endotoxin were added, similar linear results were obtained, with a mean gradient of 0.60 ± 0.062, a value significantly different from the gradient for crystalloids; $p<0.01$ using linear regression analysis. As the end point of the assay depends upon the production of a yellow colour (p-nitroaniline), it was important to validate its use in jaundiced plasma. As the absorption spectra for p-nitroaniline and bilirubin in plasma, are different, it is possible to perform the assay, but necessary to establish the influence of bilirubin on the values obtained. Using plasma from 15 jaundiced patients, the standard curves again appeared linear with a mean gradient of 0.77 ± 0.061 which was significantly different from both normal plasma and crystalloids ($p<0.01$ in both cases). Thus, although bilirubin affects the sensitivity of the assay, endotoxin concentrations may be measured in jaundiced plasma provided appropriate standards are used. Studies in patients with diverse liver disease show this assay to be simple, repeatable and sensitive (lower limit of detection = 0·1 Eu/ml).

F101

Prophylaxis of perinatal HBV transmission and its relationship with HBe antibody status and HBV-DNA

D A KELLY, D RUTTER, C GREENFIELD, P KARAYIANNIS, J MONJARDINO, M FOWLER, AND H C THOMAS *(Department of Medicine and Paediatrics, Royal Free Hospital, London)* The risk of perinatal trans-

mission of hepatitis B virus (HBV) is related to the HBe antigen/antibody status of the carrier mother. We have investigated the relationship between the HBe antigen/antibody state, the presence of HBV-DNA and the risk of perinatal transmission in 90 pregnant Kenyan women (45 HBsAg+ve; 45 HBsAg−ve). In a pilot study, we also evaluated the efficacy of combined active and passive immunisation in preventing perinatal transmission in three HBsAg carrier mothers.

In the Kenyan study, two of the Kenyan HBsAg+ve mothers were HBeAg+ve and HBV-DNA+ve; 11 women had no 'e' markers, two were DNA+ve and nine were DNA−ve; 31 mothers were anti-e+ve, nine were DNA+ve and 22 DNA−ve. Three babies (7%) were infected in the perinatal period, all mothers were anti-HBe positive, one was HBV-DNA positive and two were negative. Three babies, including one from the control group became infected at nine months, presumably from horizontal transmission.

In the pilot study, the babies of an HBeAg+ve, HBV-DNA+ve mother and two anti-HBe negative (DNA+ve (1), HBV-DNA−ve (1)) mothers were immunised with the combination of hepatitis B vaccine (Hep-Vax 0·5 ml) and hepatitis B immune globulin (HBIG–200 mg) at birth and one month and with Hep-Vax only at six months. All babies were HBsAg−ve at birth and produced a satisfactory rise in anti-HBs at one and six months. It is concluded that (i) perinatal transmission in African women is less likely than horizontal transmission; (ii) that anti-HBe may have a virus-neutralising effect as the majority of these mothers who were also HBV-DNA+ve did not infect their babies and (iii) that the combination of active and passive immunisation was both safe and effective in these high risk babies.

F102

Portal hypertension in primary biliary cirrhosis (PBC) – an early assault on the sinusoids?

T W WARNES, A SMITH, N Y HABOUBI, H ALI, V COPE, AND P VALES *(Liver Section, University Department of Gastroenterology, Manchester Royal Infirmary, Manchester)* While it is recognised that patients with PBC may present with bleeding oesophageal varices, the mechanism of portal hypertension is poorly understood. We have performed 83 WHVP determinations in 56 patients and correlated the results with recognised biochemical and histological parameters of disease progression. Liver biopsies were graded for overall Ludwig stage (I–IV). The presence and extent of regeneration nodules and central hepatic vein damage were assessed semi-quantitatively, as was pericellular fibrosis in Rappaport zone 1 (0 to +3). Non-parametric statistical methods were used. A raised serum bilirubin (>22 mol/l) was found in 46% of our PBC patients while the corrected WHVP was significantly raised ($p<0·001$) in 86% (median 13 mmHg, control median 2 mmHg). WHVP showed a significant correlation with Ludwig stage ($p<0·01$) and also with the degree of pericellular fibrosis ($p<0·005$). No significant correlation existed between pericellular fibrosis and Ludwig stage.

Portal hypertension and oesophageal varices are normally regarded as a late feature of PBC but in the majority of our patients WHVP was significantly raised, even in those who would be classified as early by conventional criteria (serum bilirubin and Ludwig stage). In 40% of our patients the WHVP was raised in the presence of a normal serum bilirubin. Thus, portal hypertension may occur with a normal serum bilirubin, in early disease (Ludwig stage I and II) and in the absence of regeneration nodules and central hepatic vein damage. The overall histological assessment suggests that portal hypertension in PBC originates at a sinusoidal rather than a post-sinusoidal level.

F103

Inadequate diet is not the only cause for vitamin C deficiency in alcoholics

R FAIZALLAH, A I MORRIS, N KRASNER, AND R J WALKER *(Gastrointestinal Unit, Walton Hospital, Liverpool)* The majority of alcoholics are vitamin C deficient. Although traditionally ascribed to inadequate dietary intake we have investigated the theoretical possibility that impaired absorption and/or increased urinary loss may be additional mechanisms. ^{14}C ascorbic acid was administered orally or intravenously to 12 non-cirrhotic alcoholic patients and 11 matched controls. Total urinary recovery was measured over a six day period, after administration of large flushing doses of 'cold' vitamin C. There was significantly less ^{14}C ascorbic acid excreted by the alcoholics after oral administration compared with controls ($p<0·01$).

Intravenous administration resulted in similar urinary excretion in both groups, suggesting that impaired absorption occurs in alcoholics. The effects of alcohol administration on urinary vitamin C excretion was investigated in nine healthy, non-alcoholic subjects who each drank nil, water, lager, and whisky in random order. The volume of water and lager administered was 1 litre/70 kg body weight, resulting in the quantity of alcohol being 0·58/kg body weight. A similar quantity of alcohol as whisky was used. The 28% reduction in vitamin C excretion with fasting ($p<0·01$) was completely abolished by drinking water. Alcohol in either form produced a 47% increase in urinary vitamin C excretion ($p<0·025$). Vitamin C deficiency in alcoholics may thus be compounded by impaired absorption and an ascorbiruesis.

F104

Prognostic factors in alcoholic cirrhosis

R BRADBEAR, W J JENKINS, D ASHBY, AND SHEILA SHERLOCK *(Departments of Medicine and Epidemiology, Royal Free Hospital School of Medicine, London)* To identify factors which influence the life expectancy of patients with alcoholic cirrhosis we analysed survival data from 138 consecutive patients admitted to this hospital in 1980 and 1981. All patients were followed until death or until the end of the study in February 1984. Clinical, laboratory and histological variables which are routinely recorded were screened and the relative risk associated with each variable was calculated.

At the end of the study 67 patients were alive and 71 dead. Only 17 deaths could not definitely be accounted for by complications of cirrhosis. The following abnormalities were found to be statistically associated with a higher risk of death; low serum albumin; high serum bilirubin; prolonged prothrombin time; high serum creatinine; ascites, gastrointestinal haemorrhage and encephalopathy on admission and during follow-up. Neither age nor sex significantly influenced survival, and continued alcohol abuse had little effect, though this may be because most patients drank little alcohol. Inflammatory activity in liver biopsy, liver size and spleen size did not affect prognosis.

A multivariate analysis of the variables screened improved discrimination of a poor prognosis and permits calculation of a

better prognostic index than a simple Child's grading.

F105

Endotoxin in portal blood – is it normal?

S BREARLEY, R I HARRIS, P STONE, AND M R B KEIGHLEY *(General Hospital and Queen Elizabeth Hospital, Birmingham)* Evaluation of the role of bacterial endotoxin in disease has been hampered by the susceptibility to contamination and relative insensitivity of most plasma endotoxin assays, and previous studies of the occurrance of portal venous endotoxaemia in health have given conflicting results. We have developed a chromogenic substrate assay sensitive to <10 pg/ml of *E coli* endotoxin in plasma in which the problem of contamination has been overcome. Using this assay 116 of 119 uninfected individuals (98%) had systemic venous endotoxin values less than 0·15 optical density (OD) units (trace amounts).

Portal and systemic blood samples were obtained from 17 patients undergoing elective upper abdominal surgery (cholecystectomy 11, vagotomy three, gastrectomy three). All samples were sterile on culture except one (diptheroid isolated). Sixteen out of 19 patients samples showed zero endotoxin activity; no sample showed activity >0·045 OD units.

We conclude that in the absence of intestinal disease or sepsis, only trace amounts of endotoxin are present in portal venous blood, and that concentrations in portal and systemic blood are similar.

F106

Interferon–α enhances non-specific cytotoxicity for autologous hepatocytes in acute and chronic hepatitis B virus (HBV) infection

M MONDELLI, A ALBERTI, G REALDI, R WILLIAMS, AND A L W F EDDLESTON *(The Liver Unit, King's College Hospital and School of Medicine & Dentistry, and Istituto di Medicina Clinica, Padua, Italy)* Controlled clinical trials are currently under way to assess the efficacy of interferon (IFN) in a variety of viral infections, including hepatitis B. Although IFN has been shown to enhance natural cytotoxicity for NK-sensitive cell lines in HBV infection, little is known of its effects when autologous hepatocytes are used as target cells. In this study, T-enriched and non-T-enriched lymphocytes from six patients with acute and six with chronic HBV infection were incubated with autologous liver cells with and without IFN-α at a concentration of 10^3 U/ml of culture medium in an 18 hour-cytotoxicity assay. Interferon-α produced a significant increase in non-T cell cytotoxicity in patients with acute and chronic hepatitis B (from 34·3±19·6% to 60·0±11·2%, $p<0·03$, and from 41·2±17·2% to 65·5±9·8%, $p<0·01$, respectively). In contrast, no significant effect was observed on T-cell-mediated cytotoxicity in either group of patients (from 39·5±11·1% to 44·2±12·9%, and from 32·3±15·1% to 33·0±16·9%, respectively). The *in vitro* effect of IFN-α was also evaluated in three patients who developed chronic NANB hepatitis after blood transfusion but no significant stimulatory effect was observed on either T- or non-T cell cytotoxicity (from 47·7±11·9% to 48·7±10·7%, and from 20·3±21·6% to 27·0±22·7% respectively). Similarly, no significant increase in cytotoxicity was noted in three control subjects. The significant enhancement of non-T cell cytotoxicity, but not of T-cell cytotoxicity, for autologous hepatocytes in HBV infection suggests that IFN-α produce a selective stimulatory effect on NK/K cells. The absence of a similar effect in patients with chronic NANB hepatitis and control subjects suggests that HBV infection alters the susceptibility of hepatocytes to interferon-stimulated NK/K cell damage.

F107

Ethinyl estradiol and medroxyprogesterone acetate induced changes in bile acid composition of rat bile

P R BAKER, G C VITALE, Y SIOW, AND A D REID *(University Department of Surgery, Ninewells Hospital & Medical School, Dundee)* Contraceptive oestrogens, such as 17α ethinyl estradiol (EE), and cancer chemotherapeutic progestogens, such as medroxyprogesterone acetate (MPA), influence certain enzyme activities of hepatic steroid metabolism which may effect the biliary output of individual bile acids, EE or MPA (5 mg/kg bw) in propylene glycol (PG), or PG alone were given subcutaneously for seven days to groups of six male Wistar rats. Rats given EE had significantly lower values for bile flow (24·0±2·8 (SD) μl/min/kg; $p<0·001$) and bile acid output (1·07±0·31 μmol/min/kg; $p<0·02$) than rats given PG alone (49·3±4·3 and 1·65±0·38) or MPA (48·3±8·0 and 1·83±0·33), while total bile acid concentration (91·2±20·7 μmol/ml/kg) was significantly higher ($p<0·05$) in EE-treated rats than in controls (66·4±10·1). Compared with rats given PG alone, EE-treated rats secreted higher proportions of tauromuricholate (26·5±3·1% and 46·2±3·4%; $p<0·001$) and glycomuricholate (6·8±1·8% and 18·3±8·8%; $p<0·02$), and lower percentages of taurocholate (36·1±3·3% and 11·9±5·6%; $p<0·001$), glycocholate (7·8±3·5% and 2·8±1·3%; $p<0·01$) and taurodeoxycholate (6·3±3·6% and 0·9±1·0%; $p<0·005$, rank sum test). Medroxyprogesterone acetate treatment produced a less pronounced but similar pattern of changes compared with control rats, with significant differences in tauromuricholate (34·5±6·1%;$p<0·02$) and taurocholate (26·4±6·2%; $p<0·01$), apart from tauroursodeoxycholate where concentrations were significantly different in the two steroid-treated groups (2·3±0·6% [EE] and 3·6±0·7% [MPA]; $p<0·01$: PG=2·8±1·3%. Steroid treated rats secreted, on average, approximately 10% of the bile acids as taurohyodeoxycholate which was higher than in controls. While the changes in individual bile acids observed in EE-treated rats could be secondary to the induced cholestasis, the altered bile acid pattern in the MPA group suggests that these clinically important steroids may have direct effects on bile acid synthesis and/or secretion.

F108

Prospective randomised controlled trial comparing somatostatin and vasopressin in the control of acute variceal haemorrhage

J N BAXTER, S A JENKINS, W A CORBETT, P DEVITT, J WARE, AND R SHIELDS *(Department of Surgery, University of Liverpool, Liverpool)* Recent studies have suggested that somatostatin (SRIF) lowers wedged hepatic venous pressure in cirrhotics and may be of value in the acute control of bleeding oesophageal varices. This study was therefore carried out to compare the efficacy of SRIF and vasopressin (AVP) in the control of acute variceal haemorrhage.

Twenty two consecutive patients admitted with endoscopically proven, actively bleeding oesophageal varices were randomised to receive intravenously either AVP (0·4 U/min) or SRIF (bolus dose of 250 μg followed by a constant infusion of 250 μg/h). The aetiology of the portal

hypertension was similar in the two groups as was the distribution of the patients among the categories of Child's classification.

Twelve patients received AVP and 10 SRIF. The initial variceal haemorrhage was successfully controlled in all 10 patients receiving SRIF. Moreover, no complications were observed in any of the 10 patients during SRIF infusion. Acute variceal haemorrhage was successfully controlled by AVP in four of the 12 patients. AVP was unsuccessful in eight patients and balloon tamponade of the oesophagus was required.

The results suggest that SRIF is more effective than AVP in controlling AVH ($p=0.003$ Fisher's exact test). Furthermore, SRIF infusion, unlike AVP administration was not associated with any compliations.

Oesophageal

F109

Outcome of gastrointestinal bleeding in subjects with varices related to source of referal

D W BULLIMORE (INTRODUCED BY M S LOSOWSKY) *(St James's Hospital, Leeds)* Studies on subjects with oesophageal varices and gastrointestinal bleeding derived from referral centres are frequently believed to be biased by the inclusion of a 'better prognosis group' – those subjects who have survived the initial bleed sufficiently well to be stabilised and transferred from an outside hospital to the referral centre. The outcome of gastrointestinal bleeding in a group of 143 subjects with oesophageal varices was assessed to determine the degree of this bias if present. All patients with varices diagnosed in the endoscopy unit and presenting with their first bleed (at this hospital) from 1973–1982 were eligible. Patient analysis included classification by original source of referral:– direct, internal (from other physicians), in-patient (i/p) external (from surrounding hospitals, 2 to 80 miles) and outpatient external. Comparisons were by life-table analysis and Fisher's test. Prognostic factors, including Child's grade, were comparable in these groups apart from more subjects with a past history of bleeding in the i/p external group (48%) compared with direct + internal group (27%), $p<0.02$. Survival of the following groups was comparable: direct *vs* i/p external ($\chi^2=0.02$, $p>0.1$ (life-table analysis to 800 days), survival to discharge 73% *vs* 76%), alcoholics (40) *vs* non-alcoholics (103) ($\chi^2=0.004$, $p>0.1$), bleeding source oesophageal varices (94) *vs* other sources and undefined (49) ($\chi^2=0.42$, $p>0.1$), i/p external group with and without previous bleed ($\chi^2=2.48$, $p>0.1$). Marked differences between groups included direct *vs* internal referrals ($\chi^2=10.52$, $p<0.005$, survival to discharge 73% *vs* 50% and to 600 days 60% *vs* 30%). Early deaths were uncommon – 8% within eight days for the direct + i/p external group. Forty four per cent of inpatient deaths were for reasons other than bleeding.

In this centre i/p external and direct referrals are similar clinically and prognostically with admission survivals of around 75% (A=93%, B=84%, C=50%). Internal referrals would in many cases probably benefit from transfer to allow a more centralised management policy.

F110

Does sclerotherapy for oesophageal varices affect oesophageal function?

J G WILLIAMS, J R TURNER, AND D BECKLY *(RN and General Hospitals, Plymouth, Devon)* The effect of endoscopic sclerotherapy for bleeding oesophageal varices on post-treatment oesophageal function has been assessed by measuring the oesophageal transit of a bolus of ^{99m}Tc sulphur colloid. Subjects were studied supine and counts were recorded using a large field of view gamma camera linked to a computer. Time activity curves were then generated from regions of interest drawn over the oesophagus and stomach.

For patients with no clinical abnormality of the oesophagus the mouth to stomach transit time for a single swallow was 7·15 sec ± 0·62 SEM (n=9). For nine patients with oesophageal varices the mean transit time was 12·44 sec ± 1·8 ($p<0.05$). The transit time was taken as the first appearance of activity in the stomach and it was notable that in most patients with varices much activity was retained in the mid and lower oesophagus. Time to clear 90% of this activity from the oesophagus was 41·5 sec ± 7 for patients with varices (n=9) compared with 9·8 sec ± 0·7 for normals. Six patients with varices were studied before and after complete obliteration of their varices by repeated endoscopic sclerotherapy. Mean arrival transit time was prolonged from 13·3 sec ± 2·8 to 16·7 sec ± 2·2 (ns). Mean clearance times were prolonged from 42·4 sec ± 4·7 to greater than 60 sec in all but one subject. Beyond one minute accurate quantitation of clearance time was impossible as computer acquisition ceased at this time. Post-treatment transit times were unrelated to symptoms or to the presence or absence of stricture on endoscopy or barium swallow.

We conclude that oesophageal transit is impaired in the presence of varices and further delay results from endoscopic sclerotherapy.

F111

Prospective study of a management protocol with early intervention for variceal bleeding in cirrhotics: possible prediction for need of sclerosis or surgery

A K BURROUGHS, M R QADIRI, G HAMILTON, C KIBBLER, G JEFFREY, K HOBBS, AND N MCINTYRE *(Depts of Medicine and Surgery, Royal Free Hospital School of Medicine, London)* Long term survival after variceal bleeding is critically determined by outcome of the acute bleed. Accepted management of variceal bleeding follows a sequential scheme from less to more invasive therapy. Variceal bleeding, however, is characterised by early repeated bleeding during the same admission. The effect of this rebleeding and timing of intervention (sclerosis or surgery) has been little studied. Prediction of rebleeding might allow earlier intervention and possibly improve prognosis. Fifty four cirrhotics (27 alcoholic) during 71 consecutive admission for variceal bleeding were studied within an ongoing protocol with strict end points for intervention (following transfusion and/or glypressin and always after tamponade). Pugh's classification on first hospital admission was used, 41 grade 'AB', 30 'C'. 48% 'AB' and 33% 'C' were haemodynamically stable on admission, and of these over 70% had not rebled at 24 hours. The remainder received glypressin, with 44% having stopped bleeding by 24 hours. Intervention within 48 hours was required in three 'AB' (7%) and 10 'C' (33%), ($p<0.01$) and subsequently in 10 'AB' and eight 'C'. Mean transfusion 7·1 units (0–20) 'AB'; 14·4 units (0–49) 'C' ($p<0.01$). Deaths in hospital (or within 30 days) 2 'AB' (5%) and 10 'C' (33%) ($p<0.2$).

This mortality rate is the lowest per admission and per patient to date. The

behaviour of 'C' patients suggests a sequential scheme of management may be inappropriate. Earlier intervention as means of improving prognosis requires evaluation. Use of discriminant analysis based in part on Pugh's criteria allows better prediction of continued or early rebleeding, and may provide a basis for more rational management of variceal bleeding.

F112

Oesophageal disorders in patients with recurrent chest pain of obscure origin

J S DE CAESTECKER, J N BLACKWELL, JOAN BROWN, AND R C HEADING *(Department of Therapeutics and Clinical Pharmacology, Royal Infirmary, Edinburgh)* Seventy one patients with recurrent chest pain were referred for oesophageal motility studies. Thirty eight had anginal pain, exercise related in 26 but occurring at rest in 12. Thirty three patients had non-anginal chest pain, including six with known ischaemic heart disease. Coronary angiograms in 27 patients showed normal coronary arteries (23), very mild disease (three) and coronary artery spasm (one). Chest pain in the remainder was considered non-cardiac in origin after clinical assessment and/or investigations which included a normal ECG with exercise. All patients underwent barium radiology and/or endoscopy before oesophageal manometry and radionuclide oesophageal transit study. Twenty seven patients underwent prolonged ambulatory intraoesophageal pH monitoring.

Abnormality was detected in 44 of the 71 patients (63% of those with anginal pain, and 64% of those with atypical pain). The final diagnoses reached were: normal oesophagus (26), gastro-oesophageal reflux (21), diffuse oesophageal spasm (16), non-specific oesophageal motility disorders (15), hypertensive lower oesphageal sphincter (four), nut-cracker oesophagus (three), and vigorous achalasia (one). Fifteen of the 21 patients with reflux also had a motility disorder. In nine of these 21, there was no endoscopic or histological evidence of oesophagitis. In six patients with normal manometry, the radionuclide transit pattern was typical of oesphageal spasm.

The results confirm the high incidence of oesophageal motor disorders in this group of patients and also show that unsuspected gastro-oesophageal reflux disease often occurs in the absence of oesophagitis. For a full assessment of such patients, manometry, radionuclide transit measurement and prolonged pH monitoring are all necessary.

F113

Intragastric bile acid concentrations in erosive oesophagitis

B J COLLINS, G CROTHERS, R J MCFARLAND, AND A H G LOVE *(Department of Medicine, The Queen's University of Belfast and The Ulster Hospital, Dundonald, Belfast)* Many patients with chronic reflux symptoms have no macroscopic oesophagitis, whereas others develop oesophageal erosions and ulcerations. It has been suggested that duodenogastric reflux of bile acids increases the cytotoxic potential of gastric juice and increases the likelihood of oesophageal damage occurring in patients with gastro-oesophageal reflux. We have measured fasting and post-prandial total bile acid concentrations after nasogastric intubation, in 16 patients with chronic reflux symptoms and erosive oesophagitis. We have also studied 16 age and sex matched control subjects. No patient or control subject had evidence of gall bladder disease. Gastric total bile acid concentrations and gastric juice pH were measured in fasting sample and at 20, 40, and 60, minutes after a corn oil test meal. At 60 minutes, gastric contents were completely aspirated. A wide inter-individual range of bile acid concentrations was detected in control subjects (0–1054 μmol/l) and patients (0–2495 μmol/l). No significant difference was detected, however, between the two groups in either fasting or post-prandial bile acid concentrations (Wilcoxon's signed rank test). Gastric juice pH values and gastric juice volumes 60 minutes after the meal did not differ between the two goups. Nine of the 16 patients had significant bile acid contamination of gastric juice (>100 μmol/l) and in seven of these the gastric juice pH was <3·5. Six of the control subjects had bile acid concentrations >100 μmol/l.

We conclude that patients with erosive oesophagitis do not have abnormal duodenogastric reflux of bile acids. Contamination of gastric juice with bile acids occurs frequently in patients and in healthy volunteers, however, and it is likely that bile acids contribute to the toxic action of gastric juice on oesophageal epithelium.

F114

Is dimethicone effective in the treatment of reflux oesophagitis?

A L OGILVIE AND MICHAEL ATKINSON *(University Hospital, Nottingham)* Dimethicone (a silicone polymer) is added to several antacids but objective proof of its efficacy is lacking. Its effectiveness was therefore assessed in a double blind controlled trial in 45 patients with endoscopically proven reflux oesophagitis. They were randomly allocated to receive either antacid-dimethicone gel (Gel AD) or an identically formulated gel containing antacid alone (Gel AA). Thirty eight patients completed the eight-week period of the study. Symptoms of gastro-oesophageal reflux were graded for severity and frequency at weeks 0, 4, and 8, while oesophagitis was assessed at weeks 0 and 8 by endoscopy, oesophageal biopsy, oesophageal motility and acid perfusion studies. Symptom scores were similar at 0, 4, and 8 in both groups and no significant differences were detected. In the assessment of oesophagitis there was a tendency for the Gel AD group to show greater improvement in endoscopic and biopsy gradings and also in the results of oesophageal motility and acid perfusion studies. When a combined overall assessment of the degree of change was calculated, patients receiving Gel AD showed a greater improvement ($p<0·02$) than the Gel AA group.

We conclude that in reflux oesophagitis the addition of dimethicone to antacids confers no symptomatic benefit, but causes improvements in the degree of oesophagitis as assessed by objective methods.

F115

Relationship between gastro-oesophageal reflux (GOR), duodenal ulcer (DU) and pyloric stenosis (PS)

D FLOOK AND C J STODDARD *(University Department of Surgery, Liverpool)* It has been suggested that gastric outlet obstruction may be an important factor in the pathogenesis of GOR. In one study 80% of patients with pyloric stenosis (PS) had endoscopic evidence of oesophagitis compared with 54% of patients with uncomplication duodenal ulcer (UD).

We have studied 64 patients undergoing elective DU surgery, of whom 12 (19%) had PS. The diagnosis of PS was based on a history of stasis vomiting and evidence of

gastric outlet obstruction on barium meal and endoscopy. Preoperatively, all 64 patients underwent upper GI endoscopy with oesophageal biopsy, oesophageal manometry and 24 hour pH studies using standard techniques.

Oesophagitis was present in three of the 12 patients with PS (25%) and in 14 of the 52 patients with an uncomplicated DU (27%). Abnormal gastro-oesophageal reflux (GOR) was demonstrated by pH monitoring in seven of the 12 patients with PS (58%) and in 32 (61%) of the remainder.

These results show that the incidence of abnormal GOR and oesophagitis in PS is no greater than in patients with an uncomplicated DU. Gastric outlet obstruction, per se, does not appear to be of major importance in the pathogenesis of GOR.

F116

Quantitative assessment of results with the Angelchik prosthesis

J H WYLLIE AND D A W EDWARDS *(Academic Unit of Surgery, Whittington Hospital, Highgate Hill, London)* Our aim was to assess the usefulness and mode of action of the Angelchik silicone antireflux prothesis in hiatal hernia and gastro-oesophageal reflux. Fifteen prostheses have been inserted and assessed more than three months later; all patients (mean age 70 years) had severe intractable symptoms of regurgitation and reflux – 12 with stricture. Hiatal flow, reflux, length and bore of strictures were quantified by standardised procedures including use of graded sizes of radio-opaque tablets. Position and orientation of the prosthesis, which part of the gut tube was encircled by it, the size and position of any intrathoracic stomach, and any evidence of angulation or compression of the gut tube were recorded on film and videotape.

Preoperatively, all had hiatal flow of barium and reflux flooding of the gullet. Postoperatively, hiatal flow could not be provoked in nine and was only slight and intermittent in six. Only in one could reflux be provoked consistently. The mean preoperative length and bore of 12 strictures were 7·5±1·74 mm (SEM) and 7·95±0·73; the mean postoperative 3·5±1·21 and 11·12±1·13 respectively; five strictures disappeared. Eight prostheses were in the chest but this did not cause symptoms or influence the results. The sphincter was not encircled by the prosthesis in any patient.

The mechanism of action cannot be a direct effect of the prosthesis on the sphincter, or the angle of His, or by compression or angulation of the gut tube by the prosthesis. The effect common to all patients was a reduction in hiatal flow. The clinical results appear to be as good as those after conventional repair.

Gastroduodenal

F117

Pharmacological evaluation of an anti-secretory agent using continuous 24 hour ambulatory gastric pH recording

B KAPUR, JANE MILLS, SARAH DUNN, KATHIE WAREHAM, W L BURLAND, M J LUNT, AND K D BARDHAN *(District General Hospital, Rotherham and Smith, Kline & French Research Ltd., Welwyn Garden City, Herts)* We have recently developed and validated a method for continuous 24 hour monitoring of intragastric pH, utilising a microelectrode and computerised data analysis. The potential of the technique in studying the effect of gastric anti-secretory drugs was evaluated, using the H_2 receptor antagonist, oxmetidine (Ox) as the example. Eight healthy subjects were studied up to four times each. They received either placebo, Ox 400 mg or 600 mg at bedtime, or 400 mg after breakfast and bedtime. The treatment order was randomised and the study conducted double-blind.

The daytime (0850–2400 hours) intragastric pH on placebo was <2·0 for 72±5% (mean±SEM) of the time and ≥4·0 for only 4±1%. On Ox, the percentage of daytime below pH 2·0 fell to 65±7%, 57±8% and 35±5% for the three doses respectively and that above pH 4·0 rose to 9±3%, 11±5% and 19±6%. These show a significant shift to higher pH with Ox ($p<0·001$) and the effect is dose related ($p<0·05$).

The nocturnal (2400–0650 hours) pH on placebo was <2·0 for 65±9% of the time and ≥4·0 for 24±9%. For the three doses of Ox, the percentage of night-time at pH <2·0 was 20±7%, 11±5% amd 20±7% and at pH≥4·0 was 56±7%, 63±9% and 56±8% respectively. These also show a significant shift to higher pH with Ox ($p<0·001$) but no dose related effect.

In conclusion, the anti-secretory effect of oxmetidine was confirmed and quantified. Compared with the traditional method involving intermittent gastric aspiration, the new technique allows more detailed analysis of the pattern of changes in intragastric pH and the study of dose related effects.

F118

Acid secretory capacity after treatment with omeprazole

B K SHARMA, P LUNDBORG, R E POUNDER, M AXELSON, M OHMAN, I A SANTANA, M TALBOT, AND C CEDERBERG *(Academic Department of Medicine, Royal Free Hospital, London, and Research Labs, AB Hassle, Molndal, Sweden)* Omeprazole is a potent suppressor of gastric acid secretion: 30 mg daily causes a 97% decrease of 24 hour intragastric acidity in duodenal ulcer patients. After 14 days of treatment with omeprazole 30–60 mg/day there is a progressive four-fold increase of fasting plasma gastrin concentration, dropping to a two-fold rise one week after stopping the drug. The object of this study was to determine whether this rise of plasma gastrin has a trophic effect on the parietal cell mass in man.

In a double-blind study, 16 healthy volunteers were studied twice before and 1, 8, 15, 22, and 57 days after, 14 daily doses of omeprazole 40 mg (n=8) or placebo (n=8). Maximal acid secretion was stimulated by intravenous pentagastrin (1·2 or 2·0 μg/kg/h), with correction for pyloric losses of acid using gastric phenol red-saline perfusion. Fasting plasma gastrin concentration was measured in duplicate samples taken before each pentagastrin test.

Every subject showed a rise in fasting plasma gastrin concentration after two weeks of treatment with omeprazole 40 mg daily. After treatment with placebo there was no change in either fasting plasma gastrin concentration or mean peak acid output. The only change in acid secretion after treatment with omeprazole was a 68% decrease of peak acid output one day after the last dose of the drug, with no evidence of a subsequent increase of acid output above the before treatment level.

In conclusion, this controlled study shows that, despite omeprazole-induced rise of fasting plasma gastrin concentration, there is no evidence of parietal cell hyperplasia.

F119

Effect of morning or evening dosage with 10 mg omeprazole on 24 hour gastric pH in duodenal ulcer patients in remission

P J PRITCHARD, N D YEOMANS, D B JONES, W J LOUIS, AND R A SMALLWOOD (INTRODUCED BY G D KERR) *(Depts of Gastroenterology and Clinical Pharmacology, Austin Hospital, Melbourne, Australia)* Omeprazole, an inhibitor of the parietal cell (H^+/K^+) ATP-ase, substantially raises gastric pH when given once/day at doses of 30–40 mg (which heal duodenal ulcers). Lower dosage (~10 mg) is being considered for maintenance therapy, but little is known about its influence on gastric pH. The aims of this study were: (1) to examine the effect of 10 mg omeprazole daily on gastric pH in duodenal ulcer patients in remission, (2) to compare the efficacy of am and pm dosage. Eight male patients aged 45–65 years received 10 mg/d (EC granulate) either in the am or pm (double-blind) for two weeks, then crossed over to the alternative regimen. Gastric pH was measured hourly for 24 hours on three occasions; baseline, and on day 14 of each dosage period. Twenty four hour median pH's (interquartile range) were 1·6 (1·4–2·1) for baseline, 3·3 (1·7–5·9) for am dose and 2·9 (1·7–5·2) for pm dosage. Differences between control and each omeprazole study were significant ($p<0·01$ Wilcoxon's paired ranks test). Despite these marked rises during treatment in the group overall, a striking feature was the intersubject variation at this dose; in two subjects, median pH did not alter during treatment, while in another it rose to 6·2 on am dosage, while for pm dosage pH was higher from 2100–0200 only.

It is concluded that 10 mg omeprazole given either am or pm raises gastric pH through the 24 hour period. The failure of two of 8 subjects to respond to this dose suggests that a higher maintenance dose may be required in some ulcer patients.

F120

Influence of haemodialysis on the antisecretory effect and oral pharmacokinetics of omeprazole in chronic renal failure

C W HOWDEN, C D PAYTON, P A MEREDITH, A I MACDOUGALL, J L REID, AND J A H FORREST *(University Department of Materia,Medica, Renal Unit and Gastroenterology Unit, Stobhill General Hospital, Glasgow)* The effects of single 30 mg oral doses of omeprazole on gastric acid secretion were assessed in six patients with chronic renal failure (CRF) receiving regular haemodialysis. Patients (age range 19–51; mean 31 years) were studied on three occasions one week apart – namely, day 1, a non-dialysis day when placebo was given; day 2, a non-dialysis day when 30 mg omeprazole was given; day 3, a dialysis day when 30 mg omeprazole was given and conventional haemodialysis was carried out over 5 hours. Basal and plateau acid output (to 1·2 μg/kg pentagastrin for one hour) (BAO, PAO) were measured on each occasion. Basal acid output (Mean±sd) on day 1 was 2·5±3·0 mmol/h. On days 2 and 3, five out of six patients were achlorhydic. Plateau acid output was 27·2±15·0 on day 1, 6·3±8·0 on day 2 (−77%; $p<0·02$) and 2·8±6·2 on day 3 (−90%; $p<0·02$). There was no significant difference between days 2 and 3.

The time to reach peak plasma concentrations (range 0·5 to 2·0 h) and the peak concentrations obtained (range 154 to 1187 μg/l) showed marked intersubject variation and were not influenced by dialysis. The area under the concentration/time curve (0–8 h) ranged from 138–3248 μg/h/l on day 2 and 99–2365 on day 3 (NS). There was no difference in omeprazole concentrations from arterial and venous samples during dialysis, and omeprazole was not detected in dialysis fluid.

Omeprazole is a powerful inhibitor of gastric acid secretion in patients with CRF, and neither its antisecretory effect nor its kinetic profile are influenced by haemodialysis.

F121

Comparison between the effects of H_2-blockers and anti-muscarinic drugs on prostaglandin generation and mucosal cell activity in the stomach of rats

D LOMANTO, E LEZOCHE, M D D'ALESSANDRO, F CARLEI, AND P MARIANI SPERANZA *(VI Clinica Chirurgica, Università Degli Studi La Sapienzà, Rome, Italy)* Cytoprotection is defined as the property of different substances of protecting the gastric mucosa against various noxious agents unrelated to the inhibition of gastric acid secretion.

Previous studies have shown that anti-muscarinic drugs may have cytoprotective activity and also H_2-blockers have been indicated as cytoprotective agents although, these results are still disputed. As prostaglandin generation is considered an important factor in gastric cytoprotection. We have compared the effects of cimetidine, ranitidine and pirenzepine on the inhibition of prostaglandin generation induced by administration of non-ulcerogenic doses of aspirin (ASA) in rats in order to elucidate the mechanism of their supposed cytoprotective activity. Five groups of rats (n=10) were studied. Groups A, B, C, and D received ASA-HCl (25 mg/kg ip) daily and group E received placebo. In addition, group A received cimetidine (28 mg/kg day), group B ranitidine (8 mg/kg day) and group C pirenzepine (28 mg/kg day). After 21 days, PGE2 content was measured by RIA on extracts from fundic mucosa, while specimens from the gastric body and antrum were stained for muco-substances (PAS technique). Semiquantitative analysis (% of PAS-positive foveolar cells) was performed.

Results show:

Group	*PGE2 (pg/100 mg) mean+SEM*	*% Inhibition PG-genesis*	*% PAS Positive foveolar cell*
A	1084+148	83*	20
B	1959+191	70·4*	35
C	2720+649	58·9*	40
D	1062+148	84*	20
E	6617+546	100*	55

* p 0·01

We conclude that in rats chronic administration of small doses ASA inhibit PGE2 generation without causing mucosal lesions in the stomach. Ranitidine as well as pirenzepine significantly antagonise these effects while cimetidine does not. Similarly ranitidine and pirenzepine but not cimetidine also modify the reduction of mucosa production induced by chronic administration of ASA.

F122

Adherent gastric mucus thickness in patients with gastroduodenal disorders

W J CUNLIFFE, A ALLEN, D A HUTTON, J P PEARSON, AND C W VENABLES *(Departments of Physiological Sciences and Surgery, University, Newcastle upon Tyne)* The gastric mucosa is covered by a layer of adherent mucus gel. This adherent mucus protects underlying epithelial cells from acid, by facilitating mucosal surface neutralisation (mucus bicarbonate barrier), from digestion by luminal pepsin and from shear forces during digestion. Previous structural studies have shown a decrease in the proportion of gel-forming polymeric glycoprotein in adherent mucus from patients with peptic ulcer disease compared with that from histologically normal stomachs. There is, however, no information concerning the continuity and depth of this mucus layer in these patients. A technique developed for measuring gastric

mucus thickness in laboratory animals has been adapted to measure adherent antral mucus thickness on mucosa in patients who have undergone gastrectomy. A minimum of 25 readings, at 500 μm intervals along three sections, were taken per patient. The adherent mucus gel in all cases was seen as a continuous opalescent layer adhering to the mucosa. Values for median thickness (n = number of patients) were as follows: duodenal ulcer, 100 μm (n=4); gastric ulcer, 250 μm (n=3); gastric cancer, 240 μm (n=6); non-diseased stomachs (Whipple's resection, Roux-en-Y for reflux oesophagitis) 180 μm (n=4). The distribution of mucus thickness measurements in duodenal ulcer patients was significantly lower compared with that in the other groups. The distribution of median thickness measurements for a group of patients with pre-pyloric ulcer (n=5) ranged in values between those obtained for duodenal ulcer and gastric ulcer patients. The thickness of mucus layer is a dynamic balance between secretion and erosion by pepsin and with respect to the thinner layer of adherent gastric mucus in duodenal ulcer patients it is relevant that pepsin concentrations are raised in this disease.

F123

Prostaglandin synthesis and catabolism in gastritis and gastric ulcer

C J HAWKEY *(Department of Therapeutics, University Hospital, Nottingham)* To assess the significance of endogenous prostaglandins (PGs) in gastritis and gastric ulcer PG synthesis and catabolism by non-ulcerated human gastric mucosa was studied.

Endoscopic biopsy specimens from 59 patients not taking anti-inflammatory drugs were homogenised on ice in Tris HCl 0·05 M pH 7·4. Aliquots (10 mg; 0·5 ml) were (a) extracted immediately; (b) incubated with arachidonic acid 2 μg for 30 min at 37°C; or (c) incubated with (9 B H_3) PGF_{2a} 1 μg (0·1 uCi) and NAD 2 mM for five min at 37°C. Histological appearances in adjacent biopsy specimens were classified (blind) as uninflamed (normal or mild gastritis) or inflamed (moderate or severe gastritis) by standard criteria.

Synthesis of PGE_2 (median and range) measured by radioimmunoassay was; (a) after homogenisation: 67 (16–465 pg/mg wet weight (n=36, uninflamed) and 122 (18–667) pg/mg (n=18, inflamed p=0·036. two tailed Mann Whitney U test); (b) after incubation with arachidonic acid: 375 (40–2262) pg/mg (n=33, uninflamed) and 460 (173–1898 pg/mg (n=17, inflamed p=0·038). Catabolism of PGF_{2a} measured by quantitative thin layer chromatography was 42% (16–66%) (n=38, uninflamed) and 30% (8–63%) (n=21, inflamed p=0·036). There was no significant differences in these values for patients with gastric ulcers compared with controls with similar levels of gastritis.

Thus, both enhanced PG synthesis and depressed PG catabolism may contribute to increased gastric PG concentrations in gastritis. No additional abnormalities of PG synthesis or of PG metabolism were found in gastric ulcer patients.

F124

Gastric juice bile acids and scintigraphy in the assessment of duodenogastric reflux

P W J HOUGHTON, N J McC MORTENSEN, W E G THOMAS, M J COOPER, A P MORGAN, AND E R DAVIES *(Departments of Surgery and Radiodiagnosis, Bristol Royal Infirmary, Bristol)* Duodenogastric reflux has been implicated in the pathogenesis of several upper gastrointestinal disorders. Scintigraphy is increasingly being used as an assessment of reflux and although the grading of reflux correlates with histological abnormalities, intragastric pH and nitrite concentrations, its accuracy is not fully established.

We have compared the grade of reflux assessed scintigraphically with the result of bile acid assay in gastric juice samples. In 104 patients undergoing review or routine gastroscopy, gastric juice was aspirated and total and free bile acids were measured. Duodenogastric reflux was then determined by milk CCK/BIDA scanning and graded 0–4 by a radiologist.

In patients with grade 0 and 1 reflux (n=40) median total bile acids were 45 μmol/l (range 0–13102) compared with grade 2 and 3 reflux patients (n=63), 2176 μmol/l (range 0–50368), p<0·001 (Mann Whitney test). Free bile acids were also lower in patients with grade 0 and 1 reflux (n=39) compared with those with grade 2 and 3 reflux (n=61); 0 μmol/l (range 0–5818) *versus* 299 μmol/l (range 0–19030), p<0·001.

These results suggest that milk CCK/BIDA scintigraphy correlates with gastric juice total bile acids and free bile acids and is a useful clinical assessment of duodeogastric reflux.

F125

Levels of n-nitroso compounds, bile acids and bacteria do not predict histological change in the operated stomach

S BREARLEY, H R THOMPSON, V POXON, D YOUNG, AND M R B KEIGHLEY *(Department of Surgery and Department of Histopathology, General Hospital, Birmingham)* N-nitroso compounds and free bile acids may be carcinogens in the operated stomach. To test this hypothesis, gastric aspirates were collected over a 24 hour period from 12 patients who had had ulcer curing operations (PVG 5, TV+P 5, TV+A 2) between one and nine years (mean four) previously and from eight healthy volunteers. Total and stable n-nitroso compounds, nitrite, total and nitrite reducing bacteria and total and free bile acids (six patients) were measured. The patients subsequently had a gastroscopy and eight biopsies were taken in a standard manner from each.

There was no significant difference between patients and controls with regard to any variable. Values varied widely between individual patients. All patients showed mild to moderate gastritis but the severity of the changes did not correlate with any variable. One patient (PVG) had a focus of intestinal metaplasia in one biopsy and three patients showed mild regenerative dysplasia. None of these had high concentrations of n-nitroso compounds, bile acids or bacteria. There was no true dysplasia.

This study has failed to find gastric metaplasia or dysplasia within the first postoperative decade even in patients with high concentrations of n-nitroso compounds, bile acids and bacteria.

F126

Gastric cancer developing after operations for benign peptic ulcer

G CORCORAN, J WARE, D DAY, AND J N BAXTER *(Royal Liverpool Hospital, University Departments of Surgery and Pathology, Liverpool)* Hitherto no large retrospective survey to identify the relative risk of gastric cancer after operations for benign peptic ulcer disease has been reported from the UK (operated stomach cancer, OSC). The Mersey Regional Cancer Registry contains the records obtained from a population of $3{\cdot}15\times10^6$. Clinical details were available for 85% of the 4296 gastric cancer registrations between 1970–1975 inclusive. From the 3638 notes reviewed,

62 OSC cases were identified (1·7%). Using regional Hospital Activity Analysis data, 7304 benign peptic ulcer operations were observed to relate to the same population and period of the survey. The annual incidence for OSC and gastric cancer *de novo* were 141 and 30 per 10^5 respectively. Thus the relative risk of developing OSC after surgery was 4·7 (95% confidence limits, 3·5–6·0). Although the mean ages of the diagnosis of OSC and gastric cancer *de novo* were similar, 66·7 years and 65·6 years respectively, the sex ratio of M:F; 3:2 for gastric cancer *de novo* was more heavily weighted for men in OSC, M:F 4:1. The mean time interval between operation and diagnosis of OSC was 21·8 years, and the crude survival was 2·2 months. Contrary to previous reports there was a duodenal ulcer predominance at the original operation (65% of those cases where details were certain, 40/62).

It is concluded: (1) there is a demonstrably increased risk of developing OSC after benign peptic ulcer surgery, and (2) contrary to previous reports, duodenal ulcer disease does not protect a patient from developing this lethal malignancy.

F127

Proximal gastric vagotomy: 5–13 years follow up

A FRESINI, P B BOULOS, AND C G CLARK *(Department of Surgery, Faculty of Clinical Sciences, University College London, The Rayne Institute, London)* Proximal gastric vagotomy (PGV) has become a standard procedure for chronic uncomplicated duodenal ulceration in specialised surgical departments. Although there is an agreement on its fewer side effects, there is still a wide discrepancy on the reported incidence of recurrent ulceration probably because of the inconsistency in which the results have been reported. In too few series, patients were followed up for an adequate period to draw out accurate conclusions.

From 1970 to 1981, 234 patients (176 men and 48 women with mean ages of 42 and 43 years repsectively) underwent PGV without drainage. There was one postoperative death (0·4%) and an overall morbidity of 20·5% owing to minor complications in 34 (14·5%) patients. The results were analysed in only 168 patients who were followed up for five to 13 years; an average of eight years. The functional result in 126 (75%) patients was good, graded as Visick I or II. Mild dumping occurred in three (1·8%) patients and mild episodic diarrhoea in five (3%) patients. The poor results in the remaining patients was because of delayed gastric emptying in seven (5%) and recurrent ulceration in 34 (20%) patients. Of the seven patients who developed gastric stasis six to 24 months after PGV, a pyloroplasty was necessary in six. Recurrent ulceration occurred within two years in 11 (32%) patients, between two and five years in 12 (35%) and in 11 (32%) after five years. The recurrences were duodenal in 25 and gastric in nine patients.

These results confirm the safety of PGV and its low rate morbitiy. Although the recurrence rate is high in this series it is within the range reported by others who followed their patients for a similar period.

F128

'Pylorospasm' induced by infusion of an endogenous opiate in man

M CAMILLERI, V STANGHELLINI, A R ZINSMEISTER, P C KAO, C H LI, AND J R MALAGELADA (INTRODUCED BY S F PHILLIPS) *(Gastroenterology Unit, Mayo Clinic, Rochester, Minnesota, and Laboratory of Molecular Endocrinology, University of California, San Francisco, California, USA)* Acute stress in man inhibits gastric emptying of a meal and increases plasma β-endorphin (β-E) concentrations. Stress-induced gastric stasis could be because of 'pylorospasm' *via* stimulation of opiate receptors. To test the hypothesis that the human pyloric sphincter is sensitive to circulating β-endorphin (β-E), we studied, in 45 healthy volunteers, the dose-related effects of iv infusion of synthetic human β-E (dose range 2·5–2500 ng/kg/min, with 1 log stepwise separation) and naloxone (N: range 114–1140 ng/kg/min, with ½ log separation) on pyloric pressure activity after a meal. We used a low-compliance pneumohydraulic perfusion system with 10 manometric sites 1 cm apart across the antroduodenal region. Plasma β-E and catecholamines were measured during the study. The pylorus was identified by manometric criteria. Statistical analysis was by an analysis of variance of surface responses programme written for the 4×5 factorial design that was used in this study.

β-E increased pyloric contractions ($p<0·01$) in the linear dose-dependent fashion up to an infusion of 250 ng/kg/min (corresponding to mean plasma concentration range of 300 to 17000 pg/ml). Naloxone alone did not alter the pyloric pressure activity; however, N significantly reduced the magnitude of pyloric response to β-E in a dose-dependent fashion ($p<0·05$). β-E also induced episodes of repetitive phasic and tonic pyloric contraction ('pylorospasm') which were not completely abolished by N. No changes were observed in plasma catecholamines.

We conclude that infusion of synthetic human β-E directly stimulates pyloric activity in man; this 'pylorospasm' may be responsible for the delayed gastric emptying induced by certain opiates and by experimental stress.

F129

Influence of intraduodenal chenodeoxycholic acid (CDC) on fasting secretory and pressure activity in the stomach and duodenum of man

I A EYRE-BROOK, N W READ, T BROWNSON, AND A G JOHNSON *(University Departments of Surgery and Physiology, Royal Hallamshire Hospital, Sheffield)* The influence of duodenal infusion of bile acid at a concentration similar to that in the common bile duct (50 mmol/l) upon fasting antroduodenal motility, duodenogastric reflux and gastric and duodenal secretion was studied in 10 healthy volunteers. Intraluminal pressures were recorded in the antrum and the first and second parts of the duodenum, and distal duodenal contents were collected by continuous low pressure sump aspiration during infusion of either saline or CDC into the second part of duodenum. Values for reflux and secretion were calculated with reference to the recovery of two non-absorbable markers infused into the stomach and duodenum. Each volunteer received at least three hour of saline and two hours of CDC infusion.

During saline infusion, duodenogastric reflux varied with the MMC, being statistically greater at the end of duodenal phase III activity than at any other time ($p<0·05$). Chenodeoxycholic acid abolished the MMC and inhibited antral contractions ($p<0·05$), but the amount of reflux was not increased compared with the saline period. Chenodeoxycholic acid also produced an increase in secretion of trypsin ($p<0·001$), bicarbonate ($p<0·001$), phospholipase A_2 ($p<0·05$) and endogenous total bile acid ($p<0·05$) into the duodenum though gastric acid secretion was unaffected. These findings suggest that bile acid may play a key role in the control of gastroduodenal motor activity and pancreatico-biliary secretion.

F130

Disordered gastric motility in chronic renal failure

B J COLLINS, P T McNAMEE, G W MOORE, C C DOHERTY, M G McGEOWN, AND A H G LOVE *(Renal Unit, Belfast City Hospital and Department of Medicine, The Queen's University of Belfast, NI)* Anorexia, nausea and vomiting almost invariably accompany advanced chronic renal failure (CRF), yet the mechanisms responsible are largely unknown. Disordered gastric motility may be associated with these symptoms, but there have been no previous studies of gastric emptying in patients with CRF. We have measured gastric emptying of a solid meal in 12 patients (GFR <5 ml/min), all of whom had normal barium meal appearances, and in 10 control subjects. The test meal consisted of 30 g porridge, mixed with 150 ml milk, and labelled with 300 μCi Technetium-99m tin colloid. Gastric emptying was monitored over a 90 minute period using a gamma camera. The retention of isotope in the stomach was significantly greater at 30, 60, and 90 minutes in the 12 CRF patients compared with the 10 control subjects ($p<0.05$) (Mann-Whitney-U test). Emptying index values were significantly smaller in the patient group compared with the control subjects, again indicating that a slower pattern of emptying occurs in CRF patients ($p<0.05$). Three of the 12 CRF patients were on regular dialysis treatment and their gastric emptying rates were similar to those of the control group.

We conclude that non-dialysed patients with chronic renal failure have impaired gastric emptying and it is possible that this disturbance improves with regular dialysis. Further assessment of this motility disorder is required as it may contribute to, or influence gastrointestinal symptoms, nutritional state and drug bioavailability in uraemic patients.

F131

Controlled trial of endoscopic bipolar electrocoagulation in the treatment of bleeding peptic ulcers

B M GOUDIE, K G MITCHELL, G G BIRNIE, AND C MACKAY *(Western Infirmary, Glasgow)* The ACMI Bicap bipolar electrocoagulation system is a portable, relatively inexpensive device which can be used in conjunction with a standard endoscope to deliver coagulating current to bleeding upper GI lesions. We have assessed its value in a double blind controlled trial.

Fifty four patients with a history of upper GI haemorrhage and endoscopic evidence of a solitary peptic ulcer with stigmata of recent haemorrhage were studied. Eight were excluded for the following reasons: poor access of the lesion in six (in four physical access was restricted and in two torrential bleeding obscured the lesion), anticoagulant therapy in one, pyloric stenosis in one. The remaining 46 were randomly allocated to electrocoagulation or sham treatment. In all patients the ulcer base was washed and those in the treatment group then had electrocoagulation performed. The 2·3 mm diameter probe was used to deliver 2 second pulses of coagulating current with a generator power setting of 7. A mean number of 8·3 applications was required to achieve charring of the ulcer base. There was no significant difference in the rate of rebleeding: treatment 7/21 (33%); control 5/25 (20%), rate of surgery: treatment 2/21 (9·5%); control 2/25 (8%), mean transfusion requirement: treatment 1·98 units; control 3·27 units or duration of hospital stay: treated 6·5 days; control 6·8 days. There were no deaths in either group. Massive bleeding complicated electrocoagulation of a visible vessel in one patient but perforation did not occur.

In conclusion the ACMI Bicap system, as used in this study, has not been found to be effective in the treatment of bleeding peptic ulcers.

F132

Inhibition of gastroduodenal fibrinolytic activity – a suggested treatment for upper gastrointestinal bleeding

S BREARLEY, V POXON, D L MORRIS, P W DYKES, AND M R B KEIGHLEY *(Department of Surgery and Department of Medicine, General Hospital, Birmingham)* Most deaths from upper gastrointestinal bleeding are associated with episodes of rebleeding. Prevention of rebleeding might be achieved by inhibiting the lysis of clot sealing the bleeding point. The ability of the protease inhibitor aprotinin to inhibit tryptic activity (measured by a BANA chromogenic substrate assay) and fibrinolytic activity (measured by a fibrin plate method) in duodenal juice was studied *in vitro*. There was a good correlation between the two variables ($r=0.8$ $p<0.05$). Trypsin becomes undetectable in the presence of aprotinin but some fibrinolytic activity persisted even at maximum concentration of the inhibitor.

The effect of aprotinin on gastric (n=5) and duodenal (n=9) juice *in vivo* was studied in healthy volunteers. Samples were collected during a control period and during intragastric infusion of aprotinin. In gastric juice trasylol reduced the mean diameter of the zone of fibrinolysis from 4·0±SD 1·3 cm to 0·5±SD 0·6 cm ($p<0.001$) and rendered trypsin undetectable.

In duodenal juice the zone of fibrinolysis was reduced from 3·8±0·8 to 2·3±0·4 cm ($p<0.001$) and tryptic activity fell from 0·92±0·25 to 0·10±0·12 mmol/ml ($p<0.02$).

Intragastric infusion of aprotinin may prove useful in preventing rebleeding following upper gastrointestinal haemorrhage.

F133

A trial design with dynamic treatment allocation for gastrointestinal bleeding

D R APPLETON, C W VENABLES, AND C O RECORD *(Department of Medical Statistics and Gastroenterology Unit, Royal Victoria Infirmary and University of Newcastle upon Tyne)* Random allocation of patients to different therapeutic modalities for life threatening conditions can suffer from the disadvantage that patients allocated to one group may fare particularly badly, so that the overall mortality during the trial is higher than would be expected after the trial was finished. To overcome this problem in the case of gastrointestinal bleeding, where potentially beneficial new treatments have recently been suggested, we have devised a dynamic allocation of peptic ulcer patients with an endoscopically visible vessel to three possible treatments – namely, (i) surgery immediately after endoscopy, (ii) endoscopic bipolar electrocoagulation, (iii) conservative treatment; if treatment (ii) or (iii) is unsuccessful surgery is performed.

The probability of being allocated to each treatment depends on the success rate to date of each treatment, on an extension of the principle that for two treatments with success rates P_1 and P_2 the relative probability of a patient receiving treatment 1 is $P_1/(1-P_1):P_2/(1-P_2)$. These probabilities are calculated by computer from a continuously updated database. Simulations have shown that with this method of biassed random allocation the proportion of patients on a less successful treatment can

be considerably lower than if allocation were completely at random, while at the same time sufficient patients receive each treatment for significant differences to be detected. This dynamic allocation procedure should be particularly valuable in situations where treatment success rates are controversial or unknown.

UPPER GI ENDOSCOPY
F134–39

F134
Design, development and testing of an endoscopic sewing machine

C P SWAIN, T N MILLS, S MARGARET ROE, AND T C NORTHFIELD *(The Department of Medical Physics, University College Hospital and Departments of Gastroenterology, St Georges Hospital, London and Ashford Hospital, Middx)* The availability of an endoscopically controlled sewing machine would enable endoscopists to perform a wide range of surgical procedures. The problems involved in the design of such a machine are not trivial. Vision is limited by the optics of the endoscope, only one side of the tissue can be reached directly, the tissue is poorly supported, power to and control of the sewing machine is *via* two small diameter biopsy channels. This study reports the design and development of an endoscopic sewing machine and its testing in the human cadaveric stomach and oesophagus. Preliminary studies established a method of 'hand sewing' *via* an endoscope using a transparent overtube with a lateral orifice to allow suction of tissue into a conformation that is easily transfixed by a threaded needle. Reliable methods of knotting are essential for secure surgery. We have developed a method of tying knots and a crimped collar method for securing thread in the gastrointestinal tract *via* endoscopes.

A prototype endoscopic sewing machine utilising two synchronously driven needles to produce a running stitch has been built and successfully tested in the human cadaveric stomach. This study has shown that sewing tissue under endoscopic contol is feasible and that the problems inherent to such a procedure can be readily overcome using either a range of new simple endoscopic tools or an endoscopic sewing machine.

F135
Sphincterotomy with gall bladder in situ; one to eight year follow up

T P YIN, J W C LEUNG, A G VALLON, AND P B COTTON *(Department of Gastroenterology, The Middlesex Hospital, London)* We have followed a total of 159 patients with gall bladders, who underwent endoscopic sphincterotomy for clearance of duct stones between 1975 and June 1983. Most had had symptoms chronically, for up to 10 years, and 43% of the patients had acute biliary symptoms (cholangitis, jaundice, pancreatitis) at the time of referral. Twenty eight per cent had other major medical problems. Sphincterotomy succeeded in 158, and the duct was clear at the end of the procedure on 142. Fifteen patients underwent early surgery for retained stones, without mortality. The remaining two died, from biliary cirrhosis and hepatic abscesses present prior to endoscopic treatment. Of the 142 patients with clear ducts, 22 underwent cholecystectomy during the same admission; three for acute cholecystitis, and 19 because of relative fitness (six of the gall bladders contained no stones). Follow up has been possible in 109 of the 121 patients who left hospital with their gall bladders; their mean age was 74 years and they had been followed between one to eight years, or earlier death. Thirty patients had died from unrelated cause, but none had died from biliary disease; nine required cholecystectomy for gall bladder symptoms (none urgently), and two needed further endoscopic duct clearance.

We confidently recommend endoscopic management for patients acutely ill with duct stones, and those who are old and frail with gall bladders. The risk of leaving the gall bladder in place appeared to be small.

F136
Development and testing of contact endoscopic thermal methods which are more effective than conventional lasers and diathermy electrodes in controlling bleeding in the gastrointestinal tract

C P SWAIN, T N MILLS, K MATTHEWSON, T C NORTHFIELD, AND P R SALMON *(Departments of Gastroenterology and Medical Physics, University College Hospital and Norman Tanner Gastroenterology Unit, St James Hospital, London)* The aim of this study was to evaluate and develop improved methods of endoscopic thermal haemostasis. We have tested three new large diameter endoscopic electrode systems comparing their performance with standard diameter electrodes. A large diameter heater probe (3·2 mm), bipolar (Bicap) and monopolar electrodes were compared with their small 2·5 mm diameter counterparts in 60 standard bleeding ulcers and on 60 large bleeding mesenteric vessels. The large bipolar and heater probe but not the monopolar probe were significantly more effective ($p<001$) than their smaller counterparts in controlling bleeding in these models and equally safe. We have designed and built (a) the first non-stick electrode using new composite plastics specifically developed by us for this purpose (b) an optional laser tip of non-stick material transparent to Nd YAG laser light designed to exert pressure on the bleeding point during photocoagulation and protect the fibre waveguide. In 40 standard canine experimental bleeding ulcers, the non-stick monopolar electrode was as highly effective as a standard monopolar electrode requiring $5·4\pm2·7$ *vs* $6·2\pm3·0$ pulses to stop bleeding. Its low thermal dissipation significantly reduced the total energy required to stop bleeding ($90\ J\pm32$ *vs* 132 ± 48, $p<0·001$), enhancing safety and tissue adherence was markedly reduced. A coaptive Nd YAG laser tip was designed to allow pressure to be exerted on a bleeding vessel during laser coagulation. In isolated arteries of 1·5–4 mm, this tip significantly enhanced occlusion, welding 12/14 (mean bursting pressure 520 mm Hg) *vs* 0/14 arteries with Nd YAG laser without coaptation.

We conclude that better mechanical occlusion of the vessel at the bleeding point by these simple means can markedly improve the performance of probe type coagulators and the laser.

F137
Endoscopic biliary prostheses for large bile duct stones

A FORBES, J W C LEUNG, AND P B COTTON *(Department of Gastroenterology, The Middlesex Hospital, London)* Most failures of endoscopic stone extraction are treated surgically. We have used endoscopic prostheses in 22 patients with strong contra-indications for surgery. Two young patients had problematic portal hypertension. The mean age of the remainder was 79 years. Ten patients had acute cholangitis. Access was limited by large diverticula in seven cases, and by Billroth II gastrectomy in four. Stones ranged in size from 15–28 mm. Nine patients had

intact gall bladders. Cholangitis recurred after prosthesis insertion in four patients, who were managed surgically (at two days and one, two, and 52 weeks); three had major peri-operative complications. Two other patients died after two months (from cirrhosis and pulmonary embolism). Stone and prosthesis passed spontaneously in one patient during the first month, and, in three asymptomatic patients, the duct was cleared at repeat ERCP after several months. Twelve patients remained well with prostheses *in situ* after follow up of 5–26 months (mean 14). Most patients had been given urso-deoxycholic acid, but its contribution is difficult to assess. Biliary prostheses may be justified in selected very high risk patients with difficult duct stones.

F138

Estimation of lactic dehydrogenase and beta-glucuronidase in gastric juice as a routine screening test for gastric cancer – a preliminary communication

P FINCH, F P RYAN, K ROGERS, AND S HOLT *(Dept of Gastroenterology, Northern General Hospital Sheffield)* In a previous presentation to this society, Rogers *et al* (1981) advanced the measurement of lactic dehydrogenase (LDH) and beta-glucuronidase (bG) in gastric wash samples as a useful test in the diagnosis of gastric cancer. In a selected population they accurately predicted 42 cancers from a group of 113 patients. We now present our findings using the same technique in a prospective group of all patients over 40 years of age undergoing routine upper GI endoscopy. Buffer was sprayed on the gastric mucosa, then retrieved for analysis of LDH, the m-isoenzyme and bG. Multiple biopsies were taken and histological examination included typing of intestinal metaplasia (IM) using mucin histochemistry. The sum of the cube roots of LDH and bG were derived and a level of 5·0 and over was taken as positive. Overall there was 52/149 (35%) positives. All six cancers (including three early gastric cancers, two malignant ulcers and one advanced cancer) were positive and only 1/20 (5%) of normal histology was positive. The remaining positives were found in patients with chronic gastritis (CG) either alone, 10/39 (26%) or with IM 21/40 (53%). Chronic gastritis + IM with dysplasia showed 4/10 (40%) positives and CG with dysplasia showed 4/8 (50%) positives. A group with no biopsy and endoscopically normal or with mild gastritis only showed 6/24 (25%) positives. No significant difference in the LDH isoenzyme ratio was found in any group. Two adenoma cases were both negative and a 'premalignant' group – for example, severe dysplasia and/or type 2B IM showed 4/4 (100%) positives.

We feel that this technique may identify patients either with early gastric cancer or those at high risk of developing cancer, and now intend to undertake a large scale prospective study to evaluate this further.

F139

Laser therapy in the management of oesophagogastric tumours

N KRASNER AND A I MORRIS *(Gastrointestinal Unit, Walton Hospital, Liverpool)* Where surgery is practicable, this must remain the treatment of choice in patients with tumours of the oesophagus and gastric cardia. In many cases, however, patients present with advanced malignancy or are too old or ill to undergo surgery. Laser irradiation offers the prospect of restoring luminal patency where obstruction by the tumour may be complete.

Twenty five patients of mean age 76 years were treated with a Nd-Yag laser set to deliver about 100 watts in pulses of 0·5 to 1·0 seconds *via* a catheter fed through the biopsy channel of a standard forward viewing panendoscope. Intravenous diazepam was used for sedation. Histology showed 17 tumours to be adenocarcinoma. Seven were squamous carcinoma and the other a leimyosarcoma. Patients underwent an average of three treatments with a mean energy applied per session of about 3000 joules. The mean survival time after the first application of the laser was 16·8 weeks (range 1 to 68 weeks). Five survived more than six months, seven for three to six months and 13 survived less than three months. Two died after oesophageal perforation consequent upon the laser procedure. A further two succumbed as a result of perforation of the oesophagus following attempted intubation when it was felt that laser therapy had no more to offer. In the majority, dysphagia was relieved after the first or second laser session and dietary restriction thereafter was minimal.

Laser treatment of oesophagogastric tumours is a palliative technique, but easily repeatable and readily tolerated by the patient. Relief of dysphagia and improvement in quality of life, even for short periods suggest that the technique is worthy of fuller consideration.

OESOPHAGUS
F140–45

F140

What is abnormal oesophageal manometry?

J N BLACKWELL, J S DE CAESTECKER, JOAN BROWN, AND R C HEADING *(Department of Therapeutics and Clinical Pharmacology, Royal Infirmary, Edinburgh)* Oesophageal manometry has gained an established role in the investigation of oesophageal disorders. Technical problems have largely been overcome and the procedure is now accurate and reproducible. Difficulties have arisen, however, in the interpretation of tracings as achalasia is the only disorder with generally accepted manometric criteria. Recognition and classification of other motor disorders have been uncertain and subjective. In an attempt to clarify the manometric features and to establish manometric criteria for diagnosis of oesophageal motor abnormalities, we have reviewed the results of 150 patients referred for manometry between 1981–1984.

The tracings were analysed by comparison with the normal values from 50 control subjects both in qualitative and quantitative terms. From this comparison the abnormalities in the patients have been grouped into manometric categories, which have previously been described but are incompletely defined and not universally accepted. We identified the following manometric groups – achalasia (eight), vigorous achalasia (two), diffuse oesophageal spasm (18), hypertensive lower oesophageal sphincter (15), nutcracker oesophagus (four), non-specific oesophageal motor disorder (20), secondary motility disorder (three), and we are able to suggest manometric criteria for these diagnoses.

The results indicate that confusion in the interpretation of oesophageal manometry can be resolved by using a standardised manometric technique coupled with knowledge of the normal range of pressures and awareness that aberrantly conducted swallows occur in normal subjects. Definite manometric abnormalities may then be classified with clarity and objectivity.

F141

Oesophageal bolus transit: effect of atropine and bethanecol on radionuclide transit (RT)

C O H RUSSELL AND D STROUD (INTRODUCED BY R G FABER) *(Departments of Surgery and Nuclear Medicine, Prince Henry's Hospital, Melbourne, Victoria, Australia)*
Manometric studies indicate IV atropine (12 μg/kg) abolishes or decreases the peristaltic response to deglutition and decreases peristaltic wave amplitude. Sub cut bethanecol (5 mg) increases wave amplitude but decreases velocity. The effect of these drugs on transit of a fluid bolus has not been studied.

The aim was to study the effect of atropine and bethanecol on oesophageal transit of a liquid radionuclide bolus.

On four separate occasions 10 fasting normal volunteers ingested 600 μCi Tc SC in 10 ml water with a single swallow, while supine over a gamma camera linked to a minicomputer. Intravenous atropine (12 μg/kg), sub cut bethanecol (5 mg), iv or sub cut saline (1 ml) preceded each study by 15, 30, 15, and 30 mins respectively and in random order. Radionuclide transit was recorded continuously for 30S.

Radionuclide transit analysed by two methods (a) region of interest (ROI) – this describes the 'pattern' of transit (normal [<15S], prolonged [>15S], impaired clearance or adynamic) by dividing the oesophageal area into three equal ROI's. Transit is analysed graphically (radioactivity *vs* time) through each ROI. (b) Average velocity – distribution of radioactivity within oesophagus calculated at regular intervals and the *average* velocity of the trailing edge of the bolus calculated and expressed in mm/S (±SD). Velocities compared with saline (control) values by paired *t*.

Saline (n=19) normal RT pattern in 19/19. Mean bolus velocity 27 mm/S (±4): bethanecol (n=10) normal RT pattern in 6/10; prolonged RT in 4/10. Mean bolus velocity 20 mm/S (±6) $p<0.01$: atropine (n=10) normal RT pattern in 1/10; impaired clearance 6/10; adynamic 3/10 Mean bolus velocity 27 mm/S (±7).

We conclude that (1) RT studies can be used to calculate bolus velocity (2) atropine (12 μg/kg) can either abolish transit or impair oesophageal clearance of the bolus without affecting the velocity of the clearing wave (3) bethanecol (5 mg) does not affect clearing efficiency of the wave but can decrease the velocity of that wave.

F142
Oesophageal dysfunction in connective tissue diseases

C O H RUSSELL, A DAVIDSON, AND G LITTLEJOHN (INTRODUCED BY R G FABER) *(Departments of Surgery and Medicine, Prince Henry's Hospital, Melbourne, Victoria, Australia)*
Oesophagitis and stricture secondary to gastro-oesophageal reflux (GER) are troublesome complications of connective tissue disorders (CTD) – especially scleroderma. The primary disease process destroys the normal mechanisms that control GER – lower oesophageal sphincter and oesophageal peristalsis – and predisposes to these complications. Identification of oesophageal motor dysfunction in patients with CTD may predict those at risk for developing oesophagitis and stricture.

Our aim is to (a) assess the prevalence of oesophageal motor dysfunction in patients with CTD using radionuclide transit (RT). (b) To test the association between abnormal RT and macroscopic evidence of oesophagitis.

Fifty four patients with CTD – 15 scleroderma (SD), 18 CRST and 21 mixed CTD – and 30 normal volunteers were prospectively studied. RT – 2×10 ml homogenous boluses of water and 400 μCi TcSC were ingested in the supine position over a gamma camera linked to a mini-computer. Transit was recorded continuously for 30S and the study repeated once in the upright posture. Transit was normal if >95% radioactivity cleared the oesophagus in <15S. Abnormal transit was graded as severe if transit time >15S in supine *and* upright posture or moderate if >15S in supine but <15S in upright posture. 15/33 SD/CRST group had endoscopy to assess macroscopic evidence of oesophagitis using standard criteria. Association between RT abnormality and oesophagitis assessed by Kappa statistic.

Abnormal RT seen in 13/15 (87%) of scleroderma group (five severe, eight moderate); 13/18 (72%) of CRST group (four severe, nine moderate); and 7/21 (33%) of mixed CTD (two severe, five moderate). Endoscopy of scleroderma/CRST group revealed oesophagitis in 6/7 with severe, 3/5 with moderate and 0/3 with no RT abnormality. There was a positive association between the presence of oesophagitis and abnormal RT ($p=0.03$).

We conclude that the preliminary results of this study would suggest an association between abnormal RT and oesophagitis ($p=0.03$) and suggest that SD/CRST patients with abnormal RT should be considered for long term anti-reflux measures.

F143
Dysphagia for solids after insertion of Angelchik prosthesis

D L MORRIS, S AMAR, J A JONES, D F EVANS, J DORAN, AND J D HARDCASTLE *(Departments of Surgery and Radiology, University Hospital, Nottingham)*
Of a prospective series of 15 patients who underwent insertion of Angelchik prostheses for gastro-oesophageal reflux, two developed complete dysphagia. In the first of these the prosthesis had rotated and displaced, requiring removal. In the second the dysphagia was because of an impacted food bolus. This prompted us to study the swallowing of solids in our remaining patients.

After a (liquid) barium swallow each patient was asked to swallow a half marshmallow washed down with a further aliquot of barium. In a normal subject this standard solid swallow can be expected to be delayed in the lower oesophagus for less than 20 seconds. Eleven of our patients consented to undergo the solid swallow.

No patient had any significant abnormality of liquid barium transit. The results of the solid swallow, however, were entirely different in that many of our patients had significant delay in transit of the solid food bolus. In order to quantify these results we have classified patients into less than 20 seconds, 20 seconds to three minutes and over three minutes. In eight of the 11 patients solid transit was slowed to over three minutes. The delay always occurred at the site of the Angelchik prothesis.

While our clinical experience of the Angelchik prosthesis has been encouraging, six patients have complained of dysphagia (of solids), and the radiographic evidence of dysphagia for solids should perhaps limit the use of this procedure until long term results are known.

F144
Lower oesophageal high pressure zone after partial fundoplication and after gastroplasty with partial fundoplication – a comparison

K JEYASINGHAM, L CHOINIERE, AND H R J PAYNE *(Department of Thoracic Surgery, Frenchay Hospital, Bristol)*
The efficiency of a high pressure zone (HPZ) created by surgical correction of gastro-oesophageal reflux is dependent not only on its location and length, but also on its ability to relax with oncoming peristalsis.

Seven patients who had undergone

partial fundoplication (group 1) in the treatment of gastro-oesophageal reflux and seven others who had undergone a gastroplasty and partial fundoplication (group 2) in the treatment of an acquired short oesophagus were evaluated manometrically.

The length of the HPZ in group 1 ranged from 1–3 cm with a mean of 2 cm. In group 2 the length varied between 2–4 cm with a mean of 2·7 cm. In both groups the HPZ was located at the level of the diaphragm. In neither group was it possible to distinguish an HPZ from the diaphragm. In both groups the HPZ showed a large diaphragmatic respiratory artifact at the onset of swallow, followed by co-ordinated relaxation which was complete. The resting tone of the HPZ in both groups ranged between 14–40 mms mercury with no significant difference between the two.

This study suggests that the HPZ created as a result of partial fundoplication, be it on its own or in conjunction with a gastroplasty, responds as a normal gastro-oesophageal sphincter does. It was not possible to separate a pre-existing gastro-oesophageal sphincter within the HPZ in either group.

F145

A clinical and pathophysiological study of a simple, safe and effective operation for the correction of resistant gastro-oesophageal reflux

A WATSON *(Department of Surgical Gastroenterology, Royal Lancaster Infirmary, Lancaster)* The ideal operation for resistant gastro-oesophageal reflux should be safe, effective, and free from complications. Objective studies have shown the Nissen fundoplication to be perhaps the most effective operation currently available, but it involves distortion of the normal anatomy and consequential mechanical complications are frequently described. For these reasons, the use of the Angelchik sialastic prosthesis has been investigated, having been the subject of recent communications to this society, but has been found also to be associated with mechanical complications and a high re-operation rate.

A more anatomical and physiologically based procedure is described which is simply performed and corrects and accentuates those factors which have been shown to influence lower oesophageal sphincter competence. This procedure has been performed over the past nine years in 188 patients with established GOR not responding to standard conservative measures. There has been no mortality, minimal morbidity and no significant mechanical complications.

The first 100 patients have been reviewed clinically after a mean follow up period of 3·4 years and graded symptomatically using a modified Visick grading. Eighty five per cent of patients came into grade I and 97% within grades I and II. More recently, the clinical studies have been complemented by pre and post-operative measurements of lower oesophageal sphincter pressure and intra-oesophageal pH, the preliminary results in 12 patients showing a mean percentage increase of 54% in lower oesophageal sphincter pressure, and on pH testing a change from a mean Tuttle score of 3 pre-operatively to 0·58 postoperatively, adding objective support to the clinical impression of the efficacy of the procedure.

COELIAC DISEASE
F146–51

F146

Parents' understanding of coeliac disease (CD) and its dietary management

P T JACKSON, J F T GLASGOW, AND R THOM *(Department of Child Health, The Queen's University of Belfast, Institute of Clinical Science, Belfast, N Ireland)* For the past 12 years CD has been diagnosed on the basis of a 'flat' jejunal biopsy and a good clinical response to strict gluten withdrawal (GFD). During this period, dietary adherance having been questioned, eight of the 50 cases in this study had had an additional compliance biopsy (CB). In the present study a standard questionnaire was given to parents of 50 (the mother in 48) children with CD, current age 1·5–19·0 years, and responses scored to give quantitative data about understanding of CD, knowledge of and attitude to the GFD and likely compliance. Twenty seven knew that the GI tract is primarily involved, 30 that CD is lifelong, 41 that gluten is to be avoided and >70% knew which of 14 common foods contain gluten. Although 1/3 considered it an 'easy' diet to maintain, in 40% adherance was less strict. Eight of 33 parents with a knowledge score (KS) of <4 had a child who previously had required CB, compared with 0/17 with a KS of 5–8 ($p=0·07$). Six of eight requiring CB, thought the diet 'easy', compared with 10/42 not requiring CB ($p<0·015$). There was no relationship between the need for CB and the number of parents at home or parental trust in the child's compliance. Knowledge score was positively correlated with – social status score ($p<0·0006$), dietary adherance ($p<0·0001$) and possession of a recent list of gluten free products ($p<0·028$) and membership of the Coeliac Society ($p<0·005$).

We conclude that 2/5 CD cases do not adhere to a GFD and in 16% there had previously been a serious problem with compliance. Parents' perception of the diet and the child's ability to comply may be at variance. More emphasis should be placed upon regular dietetic advice. Membership of the Coeliac Society should be encouraged.

F147

Non-invasive evaluation of intestinal permeability in food allergy, coeliac disease and inflammatory bowel diseases

C ANDRE, L COLIN, L DESCOS, AND S DANIERE (INTRODUCED BY R N ALLAN) *(Groupe d'Immunopathologie Digestive INSERM, Centre Hospitalier LYON SUD, Pierre Bénite, France)* Gastrointestinal permeability was investigated by the ingestion of 65 ml water containing 5 g lactulose, as a marker of abnormal absorption of large molecules, and 5 g mannitol, as a marker of absorption of small molecules. Complete five hour urine collections were made, volumes recorded and aliquot of each preserved for sugar analysis using gas chromatography. In 90 healthy fasted subjects (aged 6 months to 70 years), mean mannitol excretion was 14·11% (SD±3·56; normal lower limit >7%) and mean lactulose excretion was 0·26% (SD±0·16; normal upper limit <0·60%). The mean lactulose/mannitol ratio was 0·020 with normal upper limit 0·085.

Twenty three patients with proved food allergy as diagnosed by history and laboratory tests (prick tests, specific IgE, number of IgE intestinal plasma cells, provocation test), showed a slightly lower recovery of mannitol (mean 11·62%; SD±3·77) and a slightly higher recovery of lactulose (mean 0·39%; SD±0·29) resulting in an insignificant rise of the lactulose/mannitol ratio (mean 0·040; SD±0·030).

In seven allergic patients, intestinal

permeability was also studied immediately after the ingestion of an offending food allergen. This provocation test resulted in a 25% decrease of mannitol recovery, in a 75% increase of lactulose recovery, and in a 100% rise in the lactulose/mannitol ratio. Oral cromoglycate (300 mg before provocation test) proved in all to be completely protective both as regards symptoms and permeability abnormalities. Eight patients with coeliac disease presented marked changes: mean mannitol recovery 1·83% and mean lactulose recovery 1·41%. Their lactulose/mannitol urine excretion ratio (mean 0·610) fell to 0·110 after a three month gluten free diet resulting in partial recovery. In patients with ulcerative colitis, disease activity was associated with an increased lactulose permeability and a normal mannitol absorption. In patients with Crohn's ileocolitis, activity was associated with reduced absorption of mannitol and increased permeability to lactulose.

Measurement of intestinal permeability is of great value for the investigation of food allergy, for the management of coeliac disease and for the assessment of activity in inflammatory bowel diseases.

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Gliadin antibody secretion by coeliac jejunal mucosa

P J CICLITIRA, H J ELLIS, G M WOOD, P D HOWDLE, AND M S LOSOWSKY *(Gastrointestinal Unit, The Rayne Institute, St Thomas' Hospital and Department of Medicine, St James' Hospital, Leeds)* Untreated coeliac patients have raised circulating antibody titres to wheat gliadin and other food antigens.

Our aim is to investigate the secretion of antibodies to gliadin and casein by coeliac jejunal mucosa.

Jejunal biopsies from normal controls (10), coeliac patients on a normal diet (10), and a gluten free diet (nine) were maintained for 24 hours in organ culture. The tissue culture media were assayed for IgG, IgM, and IgA antibodies to gliadin and casein by ELISA.

Mean values and range of antibody secretion in ng per mg of tissue were: normal controls, casein IgG 2·6 (0–10·4), IgM 1·8 (0–4·7), IgA 0 (0); gliadin IgG 3·4 (0–9·2), IgM 6·2 (2·9–20·5), IgA 4·6 (0–29·7); coeliac patients on normal diet, casein IgG 4·4 (0–9·5), IgM 4·6 (0·7–12·2), IgA 1·1 (0–5·2); gliadin IgG 215·5 (5·5–2000), IgM 84·6 (4·7–360), IgA 155·9 (0–733·2); coeliac patients on gluten free diet, casein IgG 2·8 (0–8·9), IgM 8·2 (1·4–12·0), IgA 0·9 (0–3·6); gliadin IgG 6·6 (1·3–23·3), IgM 20·2 (1·0–87·9), IgA 2·7 (0·6–6·0).

Untreated coeliac jejunal mucosa secreted more IgG ($p<0·05$), IgM ($p<0·01$) and IgA ($p<0·05$) antigliadin antibodies than controls. Untreated coeliac mucosa secreted more IgG, IgM and IgA anticasein antibodies than controls but the results did not reach significance. Values for treated coeliac IgG and IgM antigliadin antibody secretion fell between controls and untreated coeliac patients and were not significantly different from either group. Treated coeliac IgA antigliadin antibodies were similar to normals and significantly lower than untreated coeliac patients ($p<0·05$). Treated coeliac anticasein antibody concentrations were similar to normals.

We conclude that raised gliadin antibody secretion by jejunal mucosa may be involved in the pathogenesis of coeliac disease.

F149

Soya protein hypersensitivity in non-responsive coeliac disease

N MIKE AND P ASQUITH *(Alastair Frazer and John Squire Metabolic and Clinical Investigation Unit, East Birmingham Hospital, Birmingham)* Ten to 15% of patients with adult coeliac disease show a suboptimal response to a gluten free diet. We have previously shown evidence of humoral and cellular immunity to soya protein in these patients. Twelve patients out of 84 with adult coeliac disease were identified who showed a poor response to gluten withdrawal. These patients remained highly symptomatic and had persisting haematological and biochemical abnormalities and malabsorption after two years or more on a strict gluten free diet. Morphometric analysis of their jejunal biopsies; while showing some improvement; showed significantly less improvement than that seen in good responder coeliacs.

Ten of these 12 patients were placed on a gluten and soya free diet. Reassessment after six monthes showed clinical improvement, a return to normal of haematological and biochemical parameters, normal intestinal absorption and statistically significant morphometric improvement in jejunal histology in nine. Jejunal morphology was now indistinguishable from those coeliacs who had shown good response to a gluten free diet. There was a significant diminution in the immune response to soya protein also.

Thus, a significant proportion of patients with coeliac disease who respond poorly to a gluten free diet have concomitant immunological hypersensitivity to soya protein causing their poor response to a gluten free diet alone.

F150

Transient gluten intolerance

J A WALKER-SMITH, A D PHILLIPS, M ROSSITER, AND B A WHARTON *(Queen Elizabeth Hospital for Children, London)* By definition, coeliac disease is a state of permanent intolerance to gluten. There is evidence that a state of transient gluten intolerance exists in infancy, presenting before the age of two years. In practice this diagnosis is usually retrospective and presumptive – that is, a child previously diagnosed as coeliac disease fails to relapse clinically and histologically after two years or more back on a gluten containing diet; McNeish *et al* have commented upon the lack of evidence to endorse this two year rule. The purpose of this paper is to describe a group of 11 children diagnosed retrospectively as transient gluten intolerance, based upon the following features: (1) initial illness associated with a small intestinal enteropathy. (2) Complete clinical remission on a gluten free diet. (3) Healing of the enteropathy on a gluten free diet. (4) Normal small intestinal mucosa two years after return to a gluten containing diet. These children have now been followed for a period from eight to 10 years. Four have had further biopsies; one was abnormal. This was seven years after return to gluten but this child clearly has coeliac disease. This finding casts doubt upon the validity of the 'two year rule' for excluding coeliac disease postgluten challenge. The remaining 10 children who all presented before 1974, have remained clinically well. This experience highlights the need to reassess the diagnosis of coeliac disease made in early infancy. Nevertheless the question must remain as to whether any of these children will eventually relapse at a later date? There is clearly a variable response to gluten in some individuals. It is known that most children with coeliac disease will relapse three months post-gluten challenge. A few will take much longer. Some appear to have had a state of temporary intolerance. Only long term

follow up with careful monitoring will determine the dietary requirements of the individual patient who fails to relapse histologically after three months of gluten challenge.

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Asthma, eczema, seasonal rhinitis and skin atopy in adult coeliac disease

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Asthma, eczema and seasonal rhinitis are reported to be more common in children with coeliac disease but there are few studies in adults. We have studied 76 patients (52 women) with treated adult coeliac disease (ACD), mean age 41 years (range 16–75), by a detailed questionnaire enquiring into personal and family history of atopic disorders. Skin hypersensitivity was determined to 21 common allergens, including 16 foods. Total serum IgE and RAST specific IgE were measured. Results have been compared with 81 age and sex matched controls with non-inflammatory gastrointestinal disorders.

A history of asthma was found in 15 (20%) ACD patients compared with four (5%) controls ($p<0.01$). Eczema and seasonal rhinitis were no more common in ACD patients themselves or their first degree relatives compared with controls. Positive prick skin tests to food and environmental allergens were more common in ACD patients compared with controls (45% compared with 27%, $p<0.05$). Two thirds of ACD patients with asthma had positive skin tests. Positive skin tests to foods were invariably associated with skin hypersensitivity to other environmental allergens and rarely occurred in isolation (4%of cases). Raised total IgE concentrations were found in similar numbers of ACD patients and controls (22%, 18% respectively) and rises of RAST specific IgE occurred only in those patients with positive skin tests.

An increased prevalence of asthma and positive skin tests has not previously been reported in ACD.

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Recurrence after sphincter saving resection for low and mid rectal cancer

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The introduction of new techniques has enabled more patients with low rectal carcinoma to undergo sphincter saving resection (SSR). This policy, however, has provoked controversy concerning the adequacy of excision and fear of increased rates of recurrence compared with abdominal perineal excision (APER). We have therefore examined our results of SSR for low and mid rectal cancers from 1978 to mid 1982.

One hundred and fifty nine patients presented with tumours less than 12 cm from the anal verge; 153 (96%) underwent resection, of whom 46 (30%) had disseminated disease. One hundred (68%) underwent SSR, 47% of whom had a stapled anastomosis, 33 (22%) had an APER and 16 (10%) had a local procedure. Operative mortality was 4% after APER and 7% after SSR. Of 74 patients undergoing radical SSR, 38 (52%) had tumours below 9 cm.

Patients were followed for a mean of 4·6 years (range 2–6 years), only four (2·5%) being lost to follow up. All surviving patients were examined for recurrence within the past six months. The incidence of recurrence after radical SSR was compared with a historical control group who underwent radical APER, matched for age, sex, Dukes' stage and height of the lesion (range 3–12 cm). The extent of histologically proven extra-rectal spread was similar in both groups. After an equivalent follow up period, overall local recurrence rates were 13·6% after SSR and 18·8% after APER. For patients with tumours below 9 cm the corresponding rates were 11·1% and 20·5%. After SSR only one recurrence was detected at the anastomotic line. Overall distant recurrence rates were 14·5% and 20% respectively. Ten patients (13·5%) died of their disease within two years of radical SSR, 15 (15%) after radical APER.

Thus, SSR does not appear to carry an increased risk of recurrent disease compared with APER after an equivalent follow up period.

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Effect of selenium and hepatic biotransformation on a potential GI tract carcinogen

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Dietary selenium has been shown to have an inverse relationship with the incidence of colon cancer. Moreover, experimental colon carcinogenesis can be inhibited with dietary excess of selenium. The mutagenic effects of 1·1 dimethylhydrazine (UDMH), a known experimental colon carcinogen, were studied in a liver perfusion/cell culture system. Male Wistar rats, fed a selenium deficient diet supplemented with Se+) or without selenium (Se−) in the drinking water were used as liver donors. The perfusate was dosed to 5 mM UDMH and Chinese hamster V79 cells were used as the genetic targets for both the perfusate and bile. Whereas UDMH *per se* caused no mutagenic effect compared with controls, the presence of livers from SE+ and Se− rats increased the observed mutagenicity by 135% and 236% respectively ($p<0.005$ for both results). Bile alone and from Se+ rat livers showed no mutagenicity, while a highly significant increase was observed in the bile of Se− rat livers (<600%, $p<0.0005$). It is known that standard commercial pellet rodent diets vary considerably in selenium content, which can explain variable results in studies of colon carcinogenesis. More important, however, are the implications of these *in vivo* findings with both a suggested relationship between higher faecal bile salt concentrations in colon cancer patients and the incidence of colon cancer being related to areas of low selenium intake.

F154

Is a circulating factor responsible for the promotion of intestinal carcinogenesis after jejunal resection in the rat?

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Small bowel resection promotes experimentally induced colonic carcinogenesis in the rat possibly by inducing a trophic response in the colon. The relationship of these effects to circulating concentrations of trophic hormonal factors has not been assessed.

Eighty male Wistar rats were randomly

allocated to four groups undergoing either jejunal transection or 20%, 50%, or 80% small bowel resection. One week after operation each rat received the first of 12 weekly subcutaneous injections of azoxymethane 10 mg/kg. Plasma enteroglucagon was measured at two and 16 weeks and on death at 26 weeeks. The number and site of tumours were recorded.

There was a significant rise in colonic tumours from 0·44±0·21/rat in the transection group to 1·24±0·24 ($p<0·02$) in the 50% resection group but falling to 0·86±0·31 in the 80% resection group. There was a six-fold increase in duodenal tumours from 0·89±0·02 in the control group to 6·0±1·27 ($p<0·05$) in the 80% resection group. In this model, ear canal tumours also occurred and these increased from 0·06±0·06 in the transection group to 0·57±0·20 ($p<0·05$) in the 80% resection group. Concentrations of the trophic hormone enteroglucagon were raised eight-fold in the 80% resection group but not raised with lesser resection. Weight gain was similar in all groups up to 16 weeks but was significantly lower in the 80% resection group at 26 weeks.

Enhancement of not only intestinal tumours but also ear canal tumours after small bowel resection suggest that a circulating factor may be responsible.

F155

Faecal sterols and colonic tumours: excretion and degradation of faecal neutral sterols in selected groups of subjects at high risk for colorectal cancer

M PONZ DE LEON, P REBECCHI, L RONCUCCI, P DI DONATO, C BERTANI, C ANNONI, C PEZCOLLER, AND N CARULLI *(Clinica Medica I and Patologia Chirurgica, Università di Modena, Modena, Italy)* Longitudinal epidemiological studies and the widespread diffusion of endoscopy allowed the identification of groups of subjects at increased risk for colorectal cancer. These groups represent an ideal model for evaulating the relative importance of putative aetiological factors. Among these, faecal sterols (both acidic and neutral) have been extensively studied but with inconclusive results. It has recently been suggested that either an increased excretion of cholesterol and its metabolites or a reduced degradation of cholesterol to coprostanol and coprostanone are frequent in subjects at high risk for colonic tumours and might be helpful parameters in the surveillance of these individuals. To get further information we studied the excretion and the degradation of neutral sterols in the following groups of subjects at risk: (A) 14 members (three affected and 11 first degree relatives) of four families with familial colonic polyposis; (B) nine subjects with solitary polyps of the colon; (C) 15 members (six affected and nine first degree relatives) of two families with a high prevalence of multiple polyps. The results were compared with those of 38 controls. The investigated subjects were kept on a standard solid diet containing a constant amount of cholesterol per day. Cr_2O_3 (300 mg/day) was also given as a marker of faecal flow. All faecal samples were collected for four to six days and individual sterols analysed by GLC.

Daily total neutral sterol excretion was not significantly different between controls and the three other investigated groups (420·4±31·5 mg/day, mean±SE, *versus* 313·4±37, 386·3±29 and 580·3±37 mg/day respectively). In all the investigated controls, cholesterol was largely converted (86·1±1·7%) to its degradation products. In the other groups most of the subjects showed a conversion pattern similar to controls, however, in a minority of them (six out of the 14 in group A, four out of nine in group B and two out of 15 in group C) cholesterol was the most abundant faecal sterol. As a whole, the conversion of cholesterol was 56±10% in group A, 56·5±13% in group B, and 82±16% in group C ($p<0·02$, $<0·01$ and ns respectively *versus* controls).

We conclude that we failed to show any significant difference in faecal neutral sterol excretion between subjects at risk for colonic cancers and controls. In the risk groups, however (but not in the controls), part of the subjects do not seem to convert cholesterol to its intestinal metabolites. It is not yet clear if this abnormality bears any relationship with the development of colorectal cancer.

F156

Detection of colon carcinoma by emission computerised tomography (ECT) using ^{123}I labelled fragments of monoclonal anti-CEA antibodies

J P GROB, B DELALOYE, A BISCHOF-DELALOYE, F BUCHEGGER, J PETTAVEL, F MOSIMANN, A BESSON, V VON FLIEDNER, AND J P MACH (INTRODUCED BY PROFESSOR F HALTER) *(Ludwig Institute for Cancer Research, Eplainges, Division of Nuclear Medicine and Dept of Surgery, Lausanne, Switzerland)* Nineteen patients with colorectal carcinoma were each injected with 1·5 mg of F(ab')2 (n=13) or Fab fragments (n=6) of monoclonal anti-CEA antibody (No 35) labelled with ^{123}I (3–4 mCi). Tomoscintigraphy was performed 6, 24 and 48 h postinjection with a dual head rotating camera. With F(ab')2 the following results were obtained. All seven primary or recurrent tumours were visualised. Two small lung metastases in a patient under chemotherapy could not be demonstrated. Of the eight patients with liver involvement four showed clearly positive, two equivocal and two negative ECT images. Image contrasts was enhanced on the 48 h pictures in the positive cases, two of them having cold areas on the six hour scan which gradually 'filled up' later on. Two patients presented eight bone metastases, and all of them were clearly detected. Thus, 18/24 tumour sites were correctly localised with F(ab')2. With Fab 4/5 primary or recurrent tumours were detected, the smallest positive tumour being a carcinomatous polyp weighing 4·5 g. Two out of two liver metastases were visualised and 18 previously unknown bone metastases in a single patient were detected. These were later confirmed by a conventional bone scan. Thus, 24/25 tumour sites were correctly localised with Fab. Our limited experience suggests that Fab fragment gives earlier and more contrasted tumour uptakes than F(ab')2 fragments. The high percentage of detected tumour sites and the excellent definition of the tumour in the positive cases represent an improvement over previously reported results.

F157

Influence of DNA abnormalities on the outcome of patients with colorectal cancer

N C ARMITAGE, R A ROBBINS, R W BALDWIN, AND J D HARDCASTLE *(Departments of Surgery and Cancer Research, University of Nottingham, Nottingham)* Nuclear chromosomal abnormality in colorectal cancer has been reported to be a marker of tumour aggressiveness. The effect on long term survival, however, has only been reported in a small number of patients. A method has been developed for recovering tumour cells from paraffin embedded material, staining the nuclei for DNA with diamino phenylindol dichloride (DAPI) and quantifying this by flow cytometry. Tumours can be divided into those whose

cells contain normal amounts of DNA (diploid) and those with abnormal DNA (aneuploid).

The DNA content of 84 primary colorectal cancers was measured from patients with at least five years follow up. The mean overall survival time of patients with aneuploid tumours (46) at 27±20·2 months was significantly worse than those with diploid cancers (38) at 43·1±19·5 months (U=490, p<0·001). Forty patients underwent curative surgery (four Dukes' Stage A, 34 Stage B, three Stage C), 13 (72%) of 18 with diploid cancers compared with only 9 (41%) of 22 with aneuploid cancers surviving five years (χ^2=4·1, p=0·04).

Forty four patients underwent non-curative surgery (12 Stage B, 23 Stage C, nine Stage D). The mean survival time of patients with aneuploid tumours (24) of 17·5±12·5 months was significantly shorter than those with diploid cancers (20) of 34·4±18·9 months. (U=101·5, p=0·001). For each Dukes stage and histological grade there was a survival advantage to those patients with diploid cancers.

Nuclear DNA content is an important prognostic factor in colorectal cancer giving a clear survival advantage to those patients with diploid cancers which appears independent of stage and histological grade.