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The 41st Annual Meeting of the British Society of Gastroenterology was held at the University of Reading, Reading, Berkshire, on 24–27 September 1980 under the Presidencies of Dr B C Morson (BSG) and Dr P B Cotton (Vice-President Endoscopy). Starting with a day devoted to specialist groups and teaching, a varied scientific programme was presented. The Plenary Session included the Sir Arthur Hurst lecture given by Sir Alan Parks on ‘Nerves, muscles and control’. Abstracts of the papers read at the meeting are printed below.

ENDOSCOPY/ THERAPY
T1—T14

T1
Endoscopy-associated outbreak of salmonellosis

B H O’CONNOR, J R BENNETT, D R SUTTON, I LEIGHTON, AND J G ALEXANDER (Department of Gastroenterology, Hull Royal Infirmary, Hull) In an endoscopy unit established 11 years ago, and now used by six alimentary endoscopists performing about 2000 examinations annually, no problems with infection had been observed until a patient developed septicaemia in January 1980 due to S. kedougou after endoscopic injection of oesophageal varices. Eleven weeks later a patient developed diarrhoea due to S. kedougou after endoscopic placement of a Celestin tube. Several other cases followed quickly. S. kedougou was isolated from 21 patients altogether, all but four having had endoscopies. Only the septicaemic patient was severely ill, and none died.

Until the outbreak was discovered endoscope cleaning had been done with 10% cetrimide. Bacteriological examination of endoscopes and accessories never produced isolates of Salmonellae. Nevertheless, the epidemiology strongly suggested that transfer of infection took place during endoscopy, presumably by one or more of the instruments or accessories (apart from four probably transmitted from patient to patient).

All instruments were sterilised by ethylene oxide, and subsequent disinfection has been by glutaraldehyde. There has been no isolation of S. kedougou since April 1980.

T2
New method for endoscopic determination of ulcer size

H DANCYGIER, D WURBS, AND M CLASSEN (introduced by M Classen) (Zentrum der Inneren Medizin, Abteilung für Gastroenterologie, Klinikum der J W Goethe Universität, Frankfurt am Main) Endoscopic estimations of ulcer size were made with forceps or graduated probe as reference lengths are unreliable.

We have adapted a computer-assisted semi-automatic device for stereological analysis for use in endoscopic determination of ulcer area.

The basic elements are a graphical measuring tablet coupled with an electronic calculator, the latter being attached to a TV-monitor. The ulcerated area can be measured directly on the TV-monitor by means of an electronic overlay marker. The path of the marker remains visible on the screen so that any surrounded lesion is exactly labelled. From the relation of a known and endoscopically introduced reference area to the ulcerated area, the latter can be calculated by the computer. It is important that the reference area lies in the plane of the ulcer, since the optical distortions for the two areas are then almost identical. Multiple measurements with different distances, different angles of viewing, and different reference areas revealed an error of 4.2±0.5%, thus documenting the reliability of this method.

T3
Unsuspected gastro-oesophageal candidiasis: an endoscopic survey

W RUMFELD, D JENKINS, AND B B SCOTT (Departments of Gastroenterology and Pathology, Lincoln County Hospital, Lincoln) Gastro-oesophageal candidiasis was formerly considered to be uncommon and to occur mainly in severely debilitated or immunosuppressed patients. In 1976 an endoscopic survey in New York found 27 cases during 370 consecutive endoscopies. In this department from January to March 1980 special search, including the use of PAS stains of biopsies, was made for this condition among all patients undergoing endoscopy. The criterion for diagnosis was tissue invasion by fungi in histological sections of the biopsies.

Nine cases were found among 108 patients. In the same series there were eight patients with simple reflux oesophagitis—that is, without candidiasis. In none of the cases was candidiasis suspected before endoscopy. At endoscopy candidiasis was suggested by white plaques in six cases. Radiology was unhelpful in any of the six cases having barium studies. Symptoms attributed to...
the candidiasis were present in only three cases. Other local pathology (peptic ulceration or carcinoma) was present in seven cases. There were five patients with oesophageal carcinoma in the series and three had candidiasis.

This study shows that, among patients undergoing endoscopy, unsuspected gastro-oesophageal candidiasis is as common as simple reflux oesophagitis and is usually associated with other local pathology, particularly oesophageal carcinoma.

T4 Sclerotherapy in the treatment of bleeding oesophageal varices

H-D Schmidt, V Daniels, H M Scheuer (introduced by M H Thompson) (Chir. Universitatsklinik Mainz, Langenbeckstr. 1, D-65, Mainz, W Germany) Sclerotherapy for bleeding oesophageal varices has recently received renewed interest. We originally used a rigid oesophagoscope with a built-in aspiration channel and an insertable optical system incorporating an injection needle at its tip. For the last year we have used a flexible endoscope exclusively, thus obviating the need for general anaesthesia.

In the past three years we have used this method in a total of 95 consecutive patients, 52 during episodes of acute haemorrhage and the remaining 43 after cessation of bleeding. Of those treated acutely, 16 died, mostly because of their underlying liver disease. Rebleeding occurred three times. There were no deaths when treatment started after the episode of bleeding. Three of these patients rebled but this was easily controlled with a further injection.

Major complications occurred in six patients: perforation of the oesophagus (one); empyema of the pleura (three); oesophagotracheal fistula (one); oesophago-aortic fistula (one). Three patients died. These complications were seen in the early phase, using the rigid oesophagoscope, and have not occurred with the use of the flexible endoscope. Sclerotherapy using a fiberoptic endoscope appears to be superior to other forms of treatment of bleeding oesophageal varices. Furthermore, this form of treatment can be used in patients with advanced liver disease.

T5 Endoscopic insertion of palliative oesophageal tubes in oesophagogastric neoplasms

D B Jones, P S Davies, and P M Smith (Department of Medicine, Llandough Hospital, Penarth, S Glamorgan) Fifty patients, aged 36–91 years (mean 72 years), underwent fibreoptic endoscopy under Valium analgesia, with attempted insertion of a Celestine tube by the Nottingham introducer for an inoperable oesophagoaortic malignant stricture. The site of the primary lesion was oesophagus in 36 patients, stomach in 12, and bronchus in two.

There were six failures of intubation, five of these occurring in gastric lesions preventing initial passage of the guidewire. There were five perforations in 46 procedures (9·2%), three patients subsequently dying and two healing spontaneously. Eight patients developed aspiration pneumonia (17·4%), and in three it probably contributed to their death. There were four tube displacements; three patients later developed bolus obstruction.

Thirty-one of the 44 successful intubations left hospital (70%) with relief of dysphagia for periods ranging from 10 days to 18 months until death (mean 5-5 months). In the 13 patients who died in hospital, six deaths occurred as a result of the procedure (mortality rate 13·6%).

We conclude that endoscopic insertion of palliative oesophagoaortic tubes is relatively safe, simple to perform, and effective in oesophageal malignant strictures. It is technically more difficult for gastric neoplasms involving the cardia.

T6 Choledochoscopic removal of bile duct stones

M H Thompson and M R Thompson (Department of Surgery, Bristol Royal Infirmary, Bristol) Choledochoscopy is an established means of confirming the clearance of bile duct stones. Modern choledochoscopes incorporate an instrument channel offering the possibility of stone removal under vision. We have used this approach in 46 consecutive explorations of the bile ducts: 41 for stones and five for strictures.

Intraduct stones were confirmed by cholangiography before exploration. Choledochoscopy was used solely as confirmation of duct clearance in eight cases; in the remainder endoscopic stone removal was attempted.

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The dormia basket removed stones in 10 of 17 attempts, and required the associated use of other methods in six of these cases. Similarly, a balloon catheter succeeded in seven of 12 cases, five in conjunction with another method. In five cases the saline flushed down the endoscope washed out all the stones, and in four cases stones were pushed onwards into the duodenum. Desjardins' forceps were still required for blind stone removal on 10 occasions, of which two were unsuccessful. The choledochoscope was particularly helpful in the management of stones in the intrahepatic ducts, but unhelpful in patients with biliary strictures.

Two patients suffered retained calculi early in the series. There were no other complications attributable to the method.

Choledochoscopy offers a safe adjunct to biliary lithotomy but endoscopic removal alone is not always possible.

T7 Choledochoscopy via the T-tube tract: an adjunct for extracting retained biliary tract stones

J G Whealin, J R Moss, and P H Wayne, III (introduced by G W Stevenson) (St Anthony Hospital and University of Louisville School of Medicine, Louisville, Kentucky, USA) Since 1973, 67 cases have been referred for treatment of residual biliary stones, mucosal defects, or strictures. In 1976 the technique of post-operative biliary tract exploration was modified in selected cases to include dilatation of the T-tube fistulous tract and choledochoscopy via the T-tube tract. Thirty-seven cases required dilatation to remove larger stones or to pass the choledochoscope.

A new T-tube has been constructed with the external limb larger than the cross-bar which permits a larger fistulous tract to form, reducing the necessity for dilatation should non-operative re-exploration become necessary. These larger fistulous tracts have closed without difficulty.

Choledochoscopy was used in 25 cases. The major advantages of choledochoscopy were to remove impacted or numerous stones and to evaluate mucosal defects. In 10 cases impacted stones were successfully removed by the endoscopic method. There were two failures from impacted stones due to limitations of the choledochoscope and current instrument designs. A higher incidence of sepsis occurred with
choledochoscopy than with the Burhenne technique.

The purpose of this paper is to discuss the advantages, limitations, and complications of cholecystoscopic via the T-tube tract. The success rate for stone extraction improved from 83% to 92% when using this modified technique.

T8 Potential dangers of mechanical bowel preparation: the risk of explosion during colonoscopic polypectomy

E W TAYLOR, S BENTLEY, D YOUNGS, AND M R B KEIGHLEY (The General Hospital, Birmingham) The explosive potential of colonic gas was recognised in 1906. Mannitol has recently been implicated as the cause of a fatal explosion during colonoscopic polypectomy. The carbohydrate load provided by mannitol might provide a mechanism for explosive gas production by proliferating microorganisms.

We have, therefore, analysed colonic gas samples aspirated at laparotomy from patients with no bowel preparation (n=11), after orthograde saline lavage (n=11), after oral mannitol (n=11), and after oral mannitol accompanied by 48 hours preoperative oral antibiotic therapy. Levels of hydrogen, methane, nitrogen, oxygen, and carbon dioxide were measured using a mass spectrometer.

Colonic gas contained significantly higher concentrations of hydrogen after oral mannitol than after orthograde saline lavage (p<0.05) and oral mannitol with antibodies (p<0.01).

Colonic gas was explosive or potentially explosive in mixtures of air in four unprepared patients, seven after oral mannitol, one after orthograde saline lavage (p<0.05), and in no patient after oral mannitol with antibodies (p<0.01).

We conclude that oral mannitol is safe before colonoscopic polypectomy if accompanied by 48 hours preoperative oral antibiotic therapy.

T9 Explosive potential of two different bowel preparations for colonoscopy

A AVGERINOS, SUSAN J LA BROOY, C FENDICK, C B WILLIAMS, AND J J MISIEWICZ (Departments of Gastroenterology, Central Middlesex Hospital and St Mark’s Hospital, London) Inflammable gases, chiefly hydrogen, are produced by bacterial fermentation of non-absorbed carbohydrate in the colon. A fatal explosion at colonoscopic polypectomy was reported because of combustible quantities of such gas. Mannitol, a non-absorbed disaccharide, was the bowel preparation used. We have examined the concentration of hydrogen in bowel gas after mannitol and compared it with castor-oil bowel preparation.

Nineteen patients undergoing colonoscopy were studied. Nine took 30 ml castor oil the night before and had tapwater enemas two hours before colonoscopy. Ten patients took 1 litre of a 10% mannitol solution at least three hours before colonoscopy. Colonoscopy was performed without insufflation or suction, using only intermittent infusions of water. Colonic gas was aspirated via an endoscopic catheter. Hydrogen concentration was measured by gas chromatography.

Four per cent concentrations of hydrogen are explosive. The mean hydrogen concentration in bowel gas samples from patients prepared with mannitol was 44 370±SEM 5958 ppm (4.4%), and with castor-oil it was 2440±241 ppm (0.24%). This difference is significant p<0.01. Colons of six of 10 patients taking mannitol, but none taking castor-oil, contained explosive concentrations of hydrogen. Mannitol bowel preparation produces significantly higher and potentially explosive concentrations of hydrogen in the colon compared with castor-oil and, if used, colonoscopic polypectomy should be performed with CO2 insufflation.

T10 Comparison of endoscopic and radiological investigation of patients with acute upper gastrointestinal bleeding

M W DRONFIELD, K D VELLACOTT, M ATKINSON, AND M J S LANGMAN (Department of Therapeutics, City Hospital, Nottingham and University Hospital, Nottingham) During a four-year period patients with acute upper gastrointestinal bleeding were randomly allocated to investigation by either fibreoptic endoscopy or double contrast barium radiology. Of 1037 patients studied, 526 had endoscopy and 511 radiology. The diagnostic yield in endoscoped patients (73%) was higher than in those x-rayed (55%) due particularly to the recognition of superficial lesions and also to the more frequent recognition of gastric ulcers by endoscopy (134) than by radiology (83). Conversely, duodenal ulcers were more commonly identified by radiology (160) than by endoscopy (122). These differences were highly significant statistically.

The mode of investigation did not influence operation rates (endoscopy 18.1%, radiology 18.2%), although operation tended to be performed earlier in patients in the endoscopy group. Mortality rates were also very similar in the two groups (endoscopy 8.4%, radiology 7.6%), and consideration of individual causes of death did not suggest that either investigation conferred special benefit in any particular patient subgroup. Thus, despite the higher diagnostic yield of endoscopy, the outcome of patients so investigated does not differ from that in patients x-rayed, and double contrast barium radiology remains a reasonable alternative investigation in patients with acute upper gastrointestinal haemorrhage.

T11 Clinical trial comparing twice-daily ranitidine with cimetidine in duodenal ulcer

R P WALT, R FROST, J TROTMAN, T H SHEPHERD, J RAWLINGS, R H HUNT, P L GOLDING, D COLIN-JONES, G J MILTON-THOMPSON, AND J J MISIEWICZ (From the Departments of Gastroenterology, Central Middlesex Hospital, London, Queen Alexandra Hospital, Portsmouth, and Royal Naval Hospital, Haslar) Cimetidine is an effective treatment for duodenal ulcer (DU). The new histamine H2-receptor antagonist ranitidine effectively inhibits 24 h H+ activity when given twice-daily. We compared ranitidine 150 mg bd with cimetidine 200 mg tds, 400 mg nocte in healing of duodenal ulcers treated for four weeks and assessed endoscopically. At three centres 98 patients were randomly allocated to two treatment groups, the endoscopists being unaware of the treatment. Concomitant serious illness, pyloric stenosis, pyloric ulceration, anti-inflammatory therapy, and previous gastric surgery were excluded. All ulcer treatments had been discontinued at least one month previously. There were no significant differences in age and sex matching between treatment groups both within and be-
between centres. Treatment began within seven days of the first endoscopy and was continued for four weeks. Routine haematology and biochemistry was undertaken before and after therapy.

Duodenal ulcers healed in 43 of 51 patients treated with cimetidine (84%) and in 40 of 52 treated with ranitidine (77%). No significant difference was found between treatments and no serious unwanted effects were reported. In duodenal ulcer healing ranitidine 150 mg bd is as effective as cimetidine 1 g daily. A twice daily dose regimen may prove an advantage with respect to patient tolerance and compliance.

T12
Does extended cimetidine treatment after duodenal ulcer healing reduce the subsequent relapse rate?

K D BARDHAN, D S COLE, B W HAWKINS, AND P C SHARPE (District General Hospital, Rotherham, and Clinical Research Department, Smith, Kline & French, Welwyn Garden City) We studied the effect of full-dose cimetidine treatment continued for a fixed period after duodenal ulcer healing on the subsequent relapse rate.

One hundred and eighty one patients whose ulcer had healed after one month on cimetidine 1 g daily were randomly allocated to three groups for further treatment with either placebo (62), or with cimetidine 1 g daily for two months (61), or for five months. Thereafter all patients received placebo. Endoscopy was done routinely every three months or earlier if symptoms recurred.

During placebo treatment, which lasted for up to 25 months, 69%, 71%, and 78% in the three groups respectively had a symptomatic ulcer recurrence. Eighty-one per cent, 80%, and 79% respectively had either a symptomatic or a silent relapse. The relapse rate was also similar in all three groups. At one, three, six, 12, and 24 months, the mean cumulative symptomatic relapse was 12%, 34%, 55%, 69%, and 72%. For either symptomatic or silent relapse, it was 14%, 46%, 69%, 79%, and 80% respectively.

Full-dose cimetidine treatment continued for some months after ulcer healing has been suggested on the assumption that it might reduce the subsequent relapse rate. However, our results show that it does not.

T13
Is ranitidine longer-acting than cimetidine?

R P WALT, D K PRICE, J RAWLINGS, R H HUNT, G J MILTON-THOMPSON, AND J J MISIEWICZ (Department of Gastroenterology, Central Middlesex Hospital, London, and Royal Naval Hospital, Haslar) Ranitidine may have a longer action compared with cimetidine, although the two drugs have a similar T1/2. We have compared the duration of activity of approximately equipotent doses of the drugs in the inhibition of meal-stimulated acid secretion. Using a technique previously described, ranitidine 150 mg was compared with cimetidine 800 mg (molar ratio 1:6:5) in five normal subjects. With Clinifeed 500 (350 ml) as stimulus diluted to 550 ml, pH 5.50, acid secretion was measured by intragastric titration with sodium bicarbonate for two hours starting immediately after intragastric administration of either drug, or placebo.

Both drugs inhibited acid secretion—ranitidine from a mean of 37.5±5.5 (mean±SEM) to 7.2±0.9 mmol/2h (81%) and cimetidine to 3.4±0.6 mmol/2h (91%). Eight hundred milligrams of cimetidine was significantly more potent than ranitidine 150 mg (p<0.01).

Secondly, five duodenal ulcer patients in remission were studied seven hours after administration of each drug using the above dosage. Drugs or placebo were administered orally with breakfast; the subjects then fasted until the test meal seven hours later. Inhibition of acid secretion occurred with both drugs, cimetidine 800 mg from 59-4 mmol/2h to 35-9 mmol/2h (40%) and ranitidine 150 mg to 39.1 mmol/2h (34%). There was no significant difference between the activities of either drugs from seven till nine hours after oral administration.

We conclude that, using this model of gastric secretion, the molar potency of ranitidine is less than 6-5 that of cimetidine and its duration of action approximately the same.

T14
Preliminary studies in man using LM 24056, a new anti-secretory agent

E J S BOYD AND K G WORMLEY (Department of Therapeutics, Ninewells Hospital, Dundee) LM 24056, a tricyclic derivative, inhibits pentagastrin- and 2-deoxyglucose-, but not histamine-, stimulated gastric secretion in experimental animals.

We have investigated its effects on pentagastrin-stimulated and overnight gastric secretion in man.

Healthy volunteers (n=5) had control basal collections for 60 minutes followed by collection of pentagastrin-stimulated (2 μg per kg/h by infusion) juice for 90 minutes, during which 150 mmol/L NaCl was infused intraduodenally. On the test day a bolus of LM 24056 200 mg was given intraduodenally followed by saline infusion. Acid output decreased by 25-6% (from 35±8.3 mmol (X±SE) to 25±5.4 mmol) during the 90 minutes and pepsin output by 22% (from 196±53 mg to 153±48 mg).

Patients with duodenal ulcer (n=10) had a light tea at 18.00 hours and gastric juice was aspirated from 21.00 h until 09.00 h the next morning. On the test night LM 24056 200 mg was given orally at 19.00 hours. Overnight acid output was reduced by 70% (from 100-2±18.3 mmol (X±SE) to 30-27±10-7 mmol) and pepsin output by 50% (from 752-1±95.3 mg to 379-9±107.3 mg). Eight patients had paired serum gastrins estimated at 20.00 hours, 24.00 hours, 04.00 hours, and 08.00 hours. Levels rose in three, remained unchanged in two, and fell in three. LM 24056 inhibits overnight acid and pepsin output and may therefore prove useful in the treatment of duodenal ulcer.

LIVER

T15
Haematin therapy for acute hepatic porphyria

K E L MCCOLL, M R MOORE, G G THOMPSON, AND A GOLDBERG (University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow) The acute hepatic porphyrias (acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria) are the result of hereditary partial enzymatic deficiencies in the pathway of haem biosynthesis. This results in a compensatory increase in the activity of the initial and rate-controlling enzyme of the pathway, delta-aminolaevulinic acid (ALA) synthase, and increased production and urinary excretion of the porphyrin precursors, ALA and porphobilinogen (PBG), and porphyrins formed proximal to the enzymatic block. The acute
porphyrias present clinically as severe and sometimes fatal attacks characterised by severe gastrointestinal disturbance often with accompanying mental disturbance and neuropathy. Over the past 10 years there have been several reports indicating beneficial response to the administration of haematin as intravenous haematin. We report our experience of haematin therapy in 13 attacks of acute porphyria in eight patients. The haematin therapy consistently lowered the urinary excretion of porphyrins and precursors by approximately 50% of the pre-haematin levels. The haematin also repressed the activity of leucocyte ALA synthase in seven of the nine patients in whom it was monitored. The clinical response was less consistent, with improvement accompanying less than half of the courses. Two patients died in attack. The haematin administration resulted in localised phlebitis in several of the patients but no other side-effects were noted.

T16
**Hepatocellular oncofetal antigen: relationship to normal human fetal ferritin**

I G MCFARLANE, S BULLOCK, W MELIA, AND ROGER WILLIAMS (The Liver Unit, King's College Hospital and Medical School, London) Previous reports have documented the presence of a 'carcinofoetal' form of ferritin in hepatocellular carcinoma tissue. In the present study, the characteristics of hepatoma ferritin have been compared with those of normal fetal liver ferritin to determine whether fetal liver might be a suitable source of material for investigation of the tumour protein.

Ferritin was purified by a standard method from 30 fetal livers (gestational ages 10 to 39 weeks) and the total ferritin, total iron and ferritin-iron content of each liver was determined by immunoelectrophoresis, atomic absorption spectrophotometry, and density gradient centrifugation as appropriate. Early gestation (<20 weeks) fetal ferritin was found to have significantly lower iron content, faster electrophoretic mobility, and a more acidic isoelectric point (by isoelectric focusing) than normal adult liver ferritin but was indistinguishable from tumour ferritin in these respects. The faster electrophoretic mobility of both fetal and tumour feritins was specifically attributable (by acid/urea gel electrophoresis) to differences in the anodic subunit of the ferritin monomer. After 20 weeks’ gestation fetal ferritin became progressively more adult in character and at 38 weeks was indistinguishable from normal adult liver ferritin.

It is concluded that early gestation (<20 weeks) fetal liver ferritin may be suitable for use in developing assays for hepatoma oncofetal ferritin.

T17
**Primary biliary cirrhosis (PBC): controlled study of epidemiology and symptom onset seasonality**

A N HAMLYN, A M MACKLON, AND O JAMES (Gastroenterology Unit, Freeman Hospital, Newcastle upon Tyne) To study factors in the presentation and occurrence of PBC a series of 115 patients was collected from NE England over 1972-80 by mortality and mitochondrial antibody survey. Comparison was made with two contemporaneous regional control series of high and low epidemicity respectively: an Echo 19 virus outbreak and acute renal failure, all causes.

Mean annual PBC diagnosis rate was 6.0/100,000 and 1980 point prevalence 4.7/100,000; 18 deaths occurred over the whole study period. Within the region prevalence varied from 1-4/10 000 in rural parts to 16-1/100 000 in inner city areas. The variation between districts in concentration areas is not statistically significant. One mother-daughter pair was recorded, no significant space-time clustering otherwise being observed. Forty-two (37%) could date symptom onset to within a precise month, peak presentation being in Spring (Kuiper's seasonality test P<0.01). Age-specific onset recruitment was linear between ages 36 and 66 years, 31 (27%) of all patients were over 65 years at first presentation. Only 10 patients (8-8%) presented in relation to specific clinical situations: pregnancy (one), oral contraceptives (one), chenic acid therapy (one), surgery (seven).

We conclude that (1) PBC is commoner and more benign than hitherto believed, (2) PBC affects the elderly as well as the middle-aged, (3) hormonal influences play a minimal part in onset, (4) PBC is of low epidemicity, but seasonality of stated symptom onset suggests the importance of an environmental triggering agency in some patients.

T18
**Defective radiocopper incorporation in early primary biliary cirrhosis (PBC)**

A N HAMLYN, M HEAPPLE, A M MACKLON, I W HAGGITH, AND O JAMES (Gastroenterology Unit, Freeman Hospital and Regional Medical Physics Centre, Newcastle General Hospital, Newcastle upon Tyne) In PBC cholestatic accumulation of hepatic copper has been thought to contribute to liver fibrosis and eventually cirrhosis. To define the mechanisms responsible for, and the stage at which, copper accumulation occurs we have investigated 20 patients at various histological stages of disease (12 of whom had been on penicillamine) and compared them with 11 control subjects. Investigations included serial determination of plasma radioactivity after intravenous #CuCl₂.

Hepatic copper content correlated poorly with biochemical indices of cholestasis. Serum copper and copper oxidase values were raised in PBC (P<0.002), irrespective of histological stage or administration of penicillamine. Plasma #Cu counts (corrected for T½) were higher in controls at 24 hours after injection and the 24/h2 plasma #Cu ratio in PBC was low with mean 1·28±0·75 (control mean 1·95±0·63, P<0·05). There was a significant difference (P<0·05) between controls and PBC in respect of regression of 24/h2 plasma #Cu ratio on serum copper oxidase, despite normal plasma stable copper/copper oxidase relationship indicating delayed or impaired incorporation of #Cu into ceruloplasmin. Two patients of 7 years with stage I (early) histology displayed abnormal radiocopper dynamics, despite otherwise normal copper indices. We conclude that in PBC a defect of copper incorporation is present in early disease and could account for some hepatic copper accumulation. Copper chelation therapy may be indicated also in some patients with stage I histology.

T19
**Hepato-intestinal extraction of zinc in liver disease**

P W N KEELING, B HANNIGAN, W RUSE, AND R P H THOMPSON (Gastrointestinal Laboratory, St Thomas' Hospital, London) Hyperzincuria has been reported in alcholic cirrhosis (AC) when hepatic zinc content may be low but does not correlate
with total body zinc stores assessed by either muscle or leucocyte zinc content. As circulating zinc is extracted by the hepatocyte we have correlated direct measurement of extraction with hepatic and leucocyte chemical zinc content.

In 10 patients, five with normal liver architecture and five with AC, undergoing transjugular liver biopsy during investigation of abnormal liver function, simultaneous peripheral (x) and hepatic (y) venous samples were obtained five, seven, and 10 minutes after intravenous injection of 5 μCi 65Zn and hepato-intestinal zinc extraction calculated as y/x x.

Zinc extraction was significantly lowered in AC (34±7.8% v 16±1±4.8%, mean±SEM, normal v AC, p<0.01).

Hepatic zinc content was reduced in AC: (249±53 v 149±25, mgZn mg⁻¹ dry weight, normal v AC, p=NS) but leucocyte zinc contents were similar (65.3±2 v 60±0.4±1 mgZn mg⁻¹ dry weight, normal v AC, p=NS). No correlation between zinc extraction and liver or leucocyte zinc content could be demonstrated.

These data suggest that in alcoholic cirrhosis hepato-intestinal extraction of zinc is severely impaired, leading to an increased spillover of zinc into the plasma pool. This may be the cause of hyperzincuria in AC.

T20
Variations in presentation of Budd-Chiari syndrome

P Powell-Jackson, W M Melia, J Canalese, and Roger Williams (Liver Unit, King's College Hospital and Medical School, London). Retrospective analysis of 36 patients (23 females, 13 males) with a proven diagnosis of Budd-Chiari syndrome revealed the absence of classical clinical features (rapid tender liver enlargement with ascites) in 33%. The typically described caudate lobe uptake on liver scanning was absent in 15%, including 11 patients with a classical presentation. Diagnosis was delayed in many patients and in eight was made only after laparotomy, which resulted in serious deterioration in four, with one death. In nine patients, the course was stuttering with apparently separate thrombotic episodes occurring at intervals of one month to six years.

Aetiological factors could be identified in 28 patients. Oral contraceptives were implicated in 11 although only two were taking them at onset of symptoms. Three had stopped because of other thrombotic complications. Primary polycythaemia was confirmed in nine but four others had raised haematocrits from plasma volume depletion. Survival from diagnosis ranged widely (two weeks to 12 years) but eight died within two months and another 12 within one year. Initial clinical findings did not influence survival but one year survival was associated with less markedly abnormal liver function tests than in patients dying within this period (p<0.005).

T21
Osteomalacia and secondary hyperparathyroidism in various forms of chronic liver disease

J B Dibble, P Sheridan, R Hampshire, G J Hardy, and M S Losowsky (Departments of Medicine and Pathology, St James's University Hospital, Leeds) Little attention has been paid to osteomalacia in chronic liver disease (CLD) other than the primarily cholestatic variety. Furthermore, in the osteomalacia of chronic cholestatic liver disease the extreme rarity of reported secondary hyperparathyroidism has raised the question of a selective resistance of bone to vitamin D, associated with hepatic impairment.

We have studied 19 patients with CLD; 10 with primarily cholestatic disease (eight primary biliary cirrhosis; two sclerosing cholangitis), and nine with other forms of chronic hepatocellular disease (one alcoholic cirrhosis; three cryogenic cirrhosis; five chronic active hepatitis). Only one patient had received vitamin D supplements.

On iliac crest biopsy, four patients (44%) in the hepatocellular group and five (50%) in the cholestatic group had osteomalacia as shown by increased osteoid, reduced calcification fronts, and low mineral apposition rates. Plasma 25 hydroxy-vitamin D was low in eight of these nine, but was also low in five out of 10 without osteomalacia.

Raised plasma parathormone levels and reduced renal tubular phosphate reabsorption gave unequivocal evidence of secondary hyperparathyroidism in five patients (56%) with osteomalacia, as would be expected in other vitamin D deficient osteomalacias.

This suggests that osteomalacia is common in non-cholestatic liver disease as well as cholestatic liver disease. The frequent finding of secondary hyperparathyroidism makes it unnecessary to postulate selective resistance of bone to vitamin D.

T22
Increases in blood brain barrier permeability after portalacaval anastomosis

A E O Zaki, D B A Silk, and Roger Williams (Liver Unit, King's College Hospital, London and Department of Gastroenterology, Central Middlesex Hospital, London). The permeability of the blood brain barrier (BBB) has been shown to increase in rats after heparctomy. The present study was undertaken to determine if similar changes occur in an animal model of chronic liver disease. The functional integrity of the BBB was determined in rats using the arterial injection-15-s decapitation Oldendorf technique six weeks after portacaval anastomosis at a time when blood ammonia levels had risen three fold (89.8±SE 4.7 μmol/l, p<0.01). Brain uptakes of 14C-L-glucose, 14C-D-sucrose, and 14C-inulin (substances which do not normally cross the barrier) were all significantly increased when compared with values in paired controls (p<0.01 for each compound). Brain uptake of the 14C-labelled aromatic amino acids tryptophan, tyrosine, and phenylalanine were also increased (p<0.01) as was that of 14C-L-leucine (p<0.01). In contrast, uptake of L-arginine was significantly reduced (p<0.01). This selective enhancement of neutral amino acid transport across the blood brain barrier could explain the abnormalities of brain serotonin and catecholamine metabolism previously noted in hepatic coma. However, the observed increase in BBB permeability could have greater relevance to the pathogenesis of chronic hepatic encephalopathy, for not only could this lead to influx of a wider range of toxic substances but also to increased efflux of essential intracerebral substrates.

T23
Influence of HLA type on development of alcoholic liver disease

J B Saunders, A D Wodak, A Haines, M Davis, and Roger Williams (Liver Unit, King's College Hospital and Medical School, London) Some studies have
shown an increased frequency of HLA-B8 in patients with alcoholic cirrhosis, and it has been inferred that individuals with this tissue type may be particularly susceptible to alcohol-induced liver damage. In the present study, we have tested this hypothesis by relating alcohol intake to HLA type in 76 patients with biopsy-proven alcoholic hepatitis or cirrhosis. Patients were interviewed using a structured questionnaire to elicit alcohol consumption during successive stages of their lives.

Twenty-two patients (28.9%) had HLA-B8. They had a significantly lower cumulative life-time alcohol consumption (879.132 kg) than patients without the antigen (1274.69 kg; \( p < 0.05 \)). Mean daily alcohol intake was not significantly different (149.3-9.8 g compared with 159.2-61 g), but patients with HLA-B8 had been drinking excessively (over 80 g ethanol per day) for a shorter period of time than patients without this antigen (13.3-2.2 years compared with 18.8-1.0 years, \( p < 0.05 \)).

This study therefore provides the first direct evidence that genetic factors linked to histocompatibility antigens are important in determining susceptibility to alcohol-induced liver disease.

T24
Does Wilson's disease result from a gene mutation resulting in perpetuation of the fetal mode of copper homeostasis into childhood?

O EPSTEIN AND S SHERLOCK (Academic Department of Medicine, Royal Free Hospital, London) Wilson's disease is due to a gene mutation causing liver copper accumulation and reduced serum copper and caeruloplasmin levels. The normal human neonate has markedly increased liver copper, but enzyme induction occurring after birth causes a fall in liver copper. We have compared serum copper and caeruloplasmin levels in 12 neonates, 10 patients with Wilson's disease, and 10 patients with primary biliary cirrhosis complicated by marked liver copper accumulation (>250 μg/g dry weight). Liver copper was measured in all the patients with Wilson's disease, and compared with neonatal liver copper levels reported in the literature.

The median serum copper in the neonates was 5.0 μmol/l, in Wilson's disease 5.9 μmol/l (NS), and in PBC, 28.5 μmol/l (normal adults 15-20 μmol/l). The median caeruloplasmin level in neonates was 0.07 g/l, in Wilson's disease 0.12 g/l (NS), and in PBC, 0.48 g/l (normal adult 0.2-0.4 g/l). Neonatal liver copper concentrations were within the Wilson's disease range.

The normal neonate has the copper profile of Wilson's disease, and differs from PBC. A gene mutation resulting in failure to induce normal copper homeostasis after birth would result in perpetuation of the fetal mode of copper homeostasis into childhood, and this could explain the aetiology and pathogenesis of Wilson's disease.

T25
Heterozygous MZ alpha-1-antitrypsin (AAT) deficiency, an important subgroup of cryptogenic cirrhosis and chronic active hepatitis (CAH) in adults

J R HODGES, H MILWARD-SADLER, AND RALPH WRIGHT (Departments of Medicine and Pathology, University of Southampton, Southampton) To determine the incidence of heterozygous AAT deficiency in adult liver disease we prospectively screened all biopsies over five years for characteristic PAS positive diastase resistant inclusions; the specificity was confirmed by immune peroxidase staining. Patients with inclusions were phenotyped. 1055 biopsies were examined, 34 contained inclusions, 25 were phenotype MZ (2-4%). Analysis of the 185 cirrhotics by histological type shows: alcoholic 84, three phenotype MZ (3-5%), CAH non-B 34, seven MZ (20-5%), cryptogenic 28, six MZ (21-4%), others 38, one MZ (2-6%). Seventy-three normal biopsies from psoriasis contained two phenotype MZ (2-7%).

The increased incidence of phenotype MZ in patients with cryptogenic cirrhosis and CAH non-B is highly significant (\( p < 0.001 \)). Features distinguishing patients with CAH non-B and AAT deficiency include older age (mean 61), absence of autoimmune diseases, negative autoantibodies, and poor steroid response. Serum AAT levels were within the normal range in half of the patients.

The finding of a high incidence of heterozygous MZ deficiency may have important implications regarding the aetiology of a subgroup of CAH and cryptogenic cirrhosis without autoimmune or virological markers. Identification of this subgroup requires meticulous examination of liver biopsies for the typical hepatocyte inclusions.

T26
HBs seroconversion in Down's syndrome and other causes of subnormality

R G CHADWICK, A HALL, R REINER, I DAVIDSON, F G BULL, R M VEALL, AND RALPH WRIGHT (Professional Medical Unit, Southampton General Hospital, and Tatchbury Mount Hospital, Southampton) Of 351 patients in a long-stay hospital for the subnormal, 26 were found to be HBsAg-positive on two occasions, 12 weeks apart. Twelve of these carriers were HBs-antigen positive by immunodiffusion.

Three years later, 21 of these carriers (six with Down's syndrome and 15 with other disorders) were available for retesting. All were still HBsAg positive. Nine were HBs-antigen positive, 10 were HBs-antibody positive, and two subjects were negative for both HBs-antigen and -antibody by radioimmunoassay. Three patients had lost HBs-antigen and had become HBs-antibody positive; none of the Down's syndrome patients had seroconverted. Eight patients who initially had been shown to be both HBs-antigen and -antibody negative by immunodiffusion were subsequently demonstrated to have HBs-antibody by radioimmunoassay.

Patients with Down's syndrome seem to seroconvert from HBs-antigen to HBs-antibody less frequently than do patients with other causes of subnormality. Many patients who are negative for both HBs-antigen and -antibody by immunodiffusion have HBs-antibody when measured by radioimmunoassay.

T27
Incidence of hepatitis B virus infection in alcoholic liver disease, HBsAg-negative chronic liver disease and primary liver cell cancer in Britain

M B BASSENDINE, L DELLA SETA, J SALMERON, H C THOMAS, AND S SHERLOCK (Department of Medicine, Royal Free Hospital, London) A study has been undertaken to determine the incidence and distribution of serum markers of hepatitis B virus (HBV) infection in British caucasian patients with biopsy-proven alcoholic liver disease (n = 56), HBsAg-negative chronic liver disease (n = 47), and primary liver cell cancer (PLCC) (n = 27), compared with an age and sex matched hospital control population (n = 112).
The 242 serum samples were examined by radioimmunoassay for HBsAg, HBeAg, and antibody to HBs, Hbc, and HBe antigens (anti-HBs, anti-Hbc, anti-HBe). No increased incidence of any serum marker of HBV infection was found in alcoholic liver disease or in 'lupoid' chronic liver disease (ANF +ve 1:40, and/or SMA +ve >1:40). In contrast, the incidence of anti-HBs and anti-HBe was significantly increased (p<0.05) in patients with 'cryptogenic' chronic liver disease. The crude relative risk of developing 'cryptogenic' chronic liver disease if anti-Hbc positive alone was 11, and if anti-HBs and anti-Hbc positive was 2.7. The incidence of HBsAg, anti-Hbc, and anti-HBe was significantly increased (p<0.005) in PLCC. The crude relative risk of developing PLCC if HBsAg positive was 17.5; if anti-Hbc positive alone was 22.5, and if anti-HBs and anti-Hbc positive was 1.3.

In conclusion, past or persistent HBV infection is an aetiological factor in some cases of 'cryptogenic' chronic liver disease and PLCC in Britain.

The British Society of Gastroenterology

T30 Radical surgery for high grade tumours of the mid-rectum

M S Elliot and R J Nicholls (introduced by Ian P Todd) (St Mark's Hospital, London) Restorative resection is being used increasingly for carcinoma of the mid-rectum, but a preoperative biopsy showing a high grade undifferentiated tumour is generally regarded as an indication for total rectal excision. To date, however, there is little evidence to suggest that this very radical form of surgery offers a higher cure rate than restorative resection.

In a retrospective study at St Mark's Hospital between 1963 and 1975 only 42 patients could be treated by a radical operation for an undifferentiated carcinoma situated between 8 and 12 cm from the anal verge. Of these, 28 underwent total rectal excision and 14 anterior resection, with no operative mortality in either group. The correct histological grading was diagnosed in only 40% of cases preoperatively. The average distal resection after restorative procedure was 2.7 cm. One patient in the group developed a pelvic recurrence (distal resection 1 cm).

There was no significant difference in the Dukes' staging, extent of local spread, or venous invasion in the two groups. Five year survival after anterior resection was 43%, after total excision 36%.

It would appear that, where radical surgery can be considered for growths at this level, anterior resection offers as good a survival as total resection.

T28 Effects of immunosuppression on hepatitis B viral replication

I V D Wellen, M F Bassendine, A K Murray, H C Thomas, and S Sherlock (Department of Medicine, Royal Free Hospital, London) Immunosuppressive therapy is widely used in the treatment of HBsAg-positive chronic liver disease with little objective evidence of benefit. A study has been undertaken to determine whether stopping or starting such therapy alters the markers of active viral replication (hepatitis B virus specific DNA polymerase activity (DNAP) and HBeAg (measured by RIA)) and HBsAg concentration in HBsAg-positive patients compared with a similar group not on therapy. Seven out of eight HBsAg-positive patients stopping therapy lost DNAP. Three lost HBeAg, one developing anti-HBe. There was a corresponding decrease in HBsAg concentration. Two out of three HBeAg-positive patients starting therapy showed an increase in DNAP and HBsAg concentration. In seven HBeAg-positive patients not on therapy there was no significant change in DNAP or HBsAg concentration and only one lost HBsAg.

In conclusion, additional HBsAg-negative patients started on immunosuppressive therapy, DNAP appeared in five, HBeAg became positive in one, and HBsAg concentration increased in four. All eight HBeAg-negative patients not on therapy showed no DNAP.

These changes in viral markers suggest that immunosuppression can potentiate hepatitis B viral replication even in the absence of HBeAg.

T29 Aprotinin therapy of gastric cancer

J G Freeman, C W Venables, G A Turner, and A L Latner (Departments of Surgery and Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne) Gastric cancer five year survival has not changed from a figure of 5-10% of cases, despite advances in surgery, anaesthesia, and cytotoxic drugs. Clearly a new mode of therapy is required and immunotherapy may be of value.

Aprotinin, a protease inhibitor, has been shown to reduce tumour invasion, spread and improve immune responses in animals, and improve cellular immunity in vivo in man. We have treated two groups of patients, (a) surgically incurable (26) and (b) surgically curable (26), with a double-blind trial of intravenous aprotinin, or placebo.

The survival of the incurable group treated by aprotinin was not significantly different at six months but the cellular immunity as measured by DNCB skin tests of the aprotinin treated group was significantly better than the placebo (p<0.002), showing that aprotinin will alter cellular immune response in vivo. At two years of follow-up the surgically cured group who received aprotinin have a survival figure of 70% compared with 38% for the placebo group (which is the expected survival at two years). Recurrences of tumour are all in the placebo treated group.

Therefore, aprotinin may be of value both as an immunotherapeutic tool and as an adjuvant therapy especially in 'surgically cured' gastric cancer.

T31 Grey-scale ultrasound scanning of the liver in the pre-operative assessment of colorectal cancer

G Lamb and I Taylor (Departments of Radiology and Surgery, Liverpool) The preoperative detection of visible liver metastases in patients with colorectal cancer is important in determining a rational treatment policy. The accuracy of hepatic ultrasound scanning (longitudinal sections) was assessed in 90 consecutive patients with primary colorectal cancer. Each patient had a 99mTc sulphur colloid scan, ultrasound scan, and liver function tests. All patients came to laparotomy and the liver was carefully palpated.

At laparotomy 15 patients (17-1%)...
had multiple metastases. These were confirmed histologically in 15. Ultrasound correctly diagnosed multiple liver metastases in 13 (86.7%). Isotopic scanning accurately diagnosed, or was highly suspicious in 14 patients with liver metastases.

There were no false positive reports on ultrasound but two were reported with isotope scan. The combination of liver scan and ultrasound scanning gave accurate information on the state of the liver in all patients in this series.

The majority of colorectal liver metastases were echogenic in appearance on ultrasound. This is in contrast with the reported appearance of metastases from other sites. Serum alkaline phosphatase was the only enzyme consistently raised in the presence of liver metastases.

In conclusion, ultrasound scanning of the liver is a simple, safe, and non-invasive method for preoperative assessment of the state of the liver in patients with primary colorectal cancer.

T32 Evidence against the theory that bile salt-binding agents may promote colon carcinogenesis

J P CRUSE, M R LEWIN, AND C G CLARK (Surgical Unit, School of Medicine, University College London, London) Bile salts are implicated in human colorectal carcinogenesis, and it has been postulated that agents which increase the delivery of bile salts to the large intestine may promote colon cancer. Aludrox binds bile salts in man and is used therapeutically for this purpose. The possibility that Aludrox may promote colon carcinogenesis was tested in vivo, using the dimethylhydrazine (DMH)-induced rat colon cancer model.

Forty-eight female Wistar rats were allocated to one of three groups, all fed the same standard diet. Group D (n=12) received DMH 40 mg/kg per week subcutaneously for 10 weeks plus drinking water ad libitum. Group DAX (n=24) received DMH as above plus Aludrox 20 mg/kg per rat/day in their drinking water. Group AX (n=12) received 10 weekly saline injections plus Aludrox as above. The survival and necropsy incidence of primary and metastatic colon cancer per group were assessed.

Fifty-six weeks after inception, all saline-injected controls were alive, while all DMH-injected rats were dead. There was no significant difference in survival or incidence of primary or metastatic colon cancer between DMH-injected rats given drinking water with or without Aludrox. The results provide reassociation that Aludrox does not promote experimental colon cancer and contradict the bile salt theory.

T33 Can the development of colorectal liver metastases be predicted?

B MOONEY, C WEST, AND I TAYLOR (Departments of Surgery and Biochemistry, Liverpool) Multiple liver metastases develop in approximately 50% of patients dying with colorectal cancer. Two studies were undertaken to assess whether preoperative clinical parameters were of predictive value in determining the subsequent appearance of hepatic secondaries.

Initially, a retrospective survey indicated that preoperative weight loss was a feature in 60% of patients who subsequently died with multiple liver metastases compared with 28.2% of patients who developed local recurrence alone. The degree of fixity of the primary tumour and histological appearance were not consistently correlated, although 80% of patients developing liver metastases had Dukes's C tumours compared with 33% in patients who developed local recurrence.

Accordingly, a prospective survey was undertaken on 93 patients without preoperative liver metastases (as determined by isotope scan and ultrasound) have been followed for up to five years. Twenty-three clinical parameters were monitored. Preoperative weight loss of greater than 6-4 kg (1 stone) (χ^2=2.53, p=0.011) and Dukes's C categorisation (χ^2=14.46, p=0.007) were the only parameters which correlated with the development of liver metastases. These factors, especially in the presence of a raised serum alkaline phosphatase value, were highly predictive of eventual macroscopic liver metastases.

A possible explanation for these findings may be that hepatic micrometastases produce clinical and biochemical changes before becoming visible on isotope scanning or palpable at laparotomy.

T34 Gastric carcinoma and pepsinogen phenotypes

A ELLIS AND S HUGHES (introduced by R B McConnell) (Gastroenterology Units of Broadgreen and Royal Liverpool Hospitals, Liverpool) Little is known of the genetic factors concerned in the pathogenesis of carcinoma of the stomach. Indeed, only one inherited factor, blood group A, is recognised. The Japanese, who have a high incidence of carcinoma of the stomach, also have a higher frequency (100%) of pepsinogen phenotype A, a genetic polymorphism of the human group I pepsinogens characterised by its absence or presence of pepsinogen 5 (phenotypes A and B respectively). In contrast, the frequency of phenotype A in a caucasian population was 85%. It was decided therefore to compare the distribution of pepsinogen phenotypes in a group of patients with a gastric neoplasm and controls.

Fifty patients (29 men, 21 women; age range 19–87 years) were phenotyped according to the method of Samloff. Forty-nine (98.0%) were phenotype A and one (2.0%) was phenotype B; whereas 436 (85.4%) of the controls were phenotype A and 74 (14.6%) were phenotype B (χ^2=6.14 p<0.02). The relative risk (Woolf) for a person of phenotype A of developing a gastric malignancy is 8.3.

We conclude that there is a significant association between gastric malignancy and pepsinogen phenotype A.

T35 Quantification of zinc in Paneth, goblet, and endocrine cells of human and rat small intestine

J GWYN JONES AND MARGARET E ELMES (Department of Pathology, University Hospital of Wales, Cardiff) Zinc can be demonstrated histochemically in rat Paneth cells using dithizone, but human Paneth cells fail to react.

X-ray microanalysis (AEI EMMA 4, Tenovus Institute, Cardiff) demonstrated zinc in both human and rat Paneth cell granules in similar amounts. The mean granule concentrations and SE were estimated in parts per million (ppm): rat jejunum, 6500±1300; rat ileum 3700±1000; human jejunum, 10 800±1800 and human ileum 2200±600. In both species higher concentrations were found in the jejunum, but a significant difference between jejunum and ileum could be demonstrated only in man (p>0.02).

Zinc was also demonstrated in goblet, enterochromaffin, and other endocrine
cell granules. The mean goblet cell granule concentration in rat ileum was 4600±1050; human jejunum, 12 300±2900, and human ileum 6500±1500. Although these values were similar to those of Paneth cells, a significant difference between Paneth and goblet cells was shown in human ileum (p>0.05). Enterochromaffin and other endocrine cell granules contained high concentrations of zinc ranging from 19 000 to 44 000 ppm.

These results demonstrate the presence of non-dithizone-reactive zinc in human Paneth cells and suggest that zinc may have an essential function in secretory cells. This may explain the abnormal Paneth cells in the congenital zinc deficiency of acrodermatitis enteropathica.

T36 Zinc deficiency in Crohn's disease, the role of biochemical monitoring and zinc requirements during intravenous nutrition (IVN)

A MAIN, M J HALL, R J MORGAN, J F MACKENZIE, A SHENKIN, G S FELL, AND R I RUSSELL (Gastroenterology Unit and Department of Biochemistry, Royal Infirmary, Glasgow) Patients with Crohn's disease may be zinc deficient and at particular risk during intravenous nutrition. The aims of this study were to detect zinc deficiency in Crohn's patients requiring IVN, to assess zinc status during IVN, and to determine the role of biochemical monitoring in assessing zinc requirements.

Ten patients requiring 14 periods of IVN (two to eight weeks)—total 59 patient-weeks—were studied by measuring serum and 24 hour urine zinc levels. Daily zinc intake was determined for each patient-week of IVN. The patient-weeks were subdivided into three groups according to zinc intake (<50, 51–100, >100 μmol zinc/day). Serum zinc levels (mean±SEM) were lower in the Crohn's group (9·9±1·0 μmol/l) than in controls (13·2±3·9) (p<0·01). During IVN there was no difference between serum zinc levels in the low intake (9·4±1·0) and the two higher intake groups (11·0±0·8; 10·5±0·4). Urine zinc levels were similar in the three intake groups but some very high levels were seen.

We concluded that (1) hypozincaeimia is a feature of severe Crohn's disease; (2) serum zinc levels are not a useful guide to zinc requirements during IVN.

In practice, in moderately ill patients, a supplement of between 50 and 100 μmol of zinc daily is sufficient to prevent zinc levels falling in anabolic patients on IVN.

T37 Tissue zinc status in patients with chronic liver disease

P W N KEELING, W RUSE, R B JONES, P J HILTON, AND R P H THOMPSON (Gastrointestinal Laboratory, and Renal Laboratory, Department of Medicine, St Thomas' Hospital, London) Accurate assessment of zinc intracellular and extracellular zinc levels requires measurement of its intracellular content or some extracellular measurement that reflects intracellular changes. Reports suggest that patients with chronic liver disease are zinc deficient on the basis of decreased plasma concentrations and hepatic content of zinc; interpretation of these measurements, however, depends upon the serum albumin concentration and the hepatic fibrous tissue content.

We have therefore measured the zinc content of leucocytes, liver at liver biopsy and postmortem (PM), and muscle at elective abdominal surgery and PM biopsy specimens, in control patients (CP) with essentially histologically normal liver tissue and in patients with chronic liver disease (CLD); primary biliary cirrhosis (PBC); active chronic hepatitis (ACH), and alcoholic cirrhosis (AC).

The results demonstrate that mean leucocyte zinc (CP, n=50, 72·6±7 v PBC, n=15, 61·4±8·9, p<0·01; ACH, n=12, 57·3±10, p<0·01; AC, n=40, 59·9±6·6 ngZn. mg−1 DW, p<0·01; mean±SD), liver (CP, n=24, 278±62 v PBC, n=5, 308±120, p=NS; ACH, n=6, 211±52, p<0·05; AC, n=34, 118±62·2 ngZn. mg−1 DW, p<0·025) were decreased in patients with CLD, except for liver zinc in PBC. Thus patients with CLD are nucleated tissue zinc deficient, but liver zinc did not correlate with the measures of extrahepatic tissue zinc status. In PBC liver zinc is normal.

T39 Components of dietary fibre reduce iron absorption

S F PHILLIPS AND R FERNANDEZ (Gastroenterology Unit, Mayo Clinic, Rochester, Minnesota, USA) Various components of dietary fibre bind calcium and iron salts in vitro, but to differing degrees. Such interactions might affect the bioavailability of heavy metals in the diet. We tested the hypothesis that components of fibre will reduce intestinal absorption of Fe3+, using dogs with chronic Thiry-Vella fistulae of upper small intestine. Test solutions contained NaCl, PEG 4000, and equimolar 59Fe SO4 and ascorbate (0·18 μM each); they were pH 5·0 and 290 mOs/ml. Lignin, cellulose, pectin, or hemicellulose were added in amounts calculated to mimic those developed in chyme. In eight experiments (two dogs), absorption of 59Fe was reduced significantly (60%) by lignin, but
was unaffected by cellulose. In addition, four dogs were tested when anaemic (haemoglobin <11.0 g/dl) and when not. Hemicellulose and pectin each reduced 59Fe absorption by 40-60% in healthy dogs (p<0.001). However, when anaemia augmented the basal level of 59Fe absorption, hemicellulose still reduced absorption significantly (20-50%) but pectin had no effect. The order of potency for reduction of iron absorption (liginin and hematicellulose > cellulose and pectin) was in accord with the degrees of iron binding in vitro. We conclude that certain components of fibre reduce the bioavailability of iron. This finding has potential implications to the widespread use of dietary supplements of fibre.

T40
Elemental and polymeric tube feeding in patients with normal gastrointestinal function: a controlled trial

B J M Jones, R Lees, J Andrews, P Frost, and D B A Silk (Departments of Gastroenterology, Dietetics, and Chemical Pathology, Central Middlesex Hospital, London) Elemental diets have been advocated for most conditions requiring enteral nutrition, including those with normal gastrointestinal function where no evidence exists that elemental diets are superior to whole protein feeds. In this controlled clinical trial, an isonitrogenous tube feed of either the elemental (Vivonex HN=VHN) or polymeric (Clinifeed 400=CF) diet was given, the calorie: nitrogen ratio being adjusted to 200:1 using the glucose polymer Caloreen. Depending upon nitrogen balance studies, either 9:6 or 14:4 g nitrogen/day was administered.

Of the 73 patients randomised 26 received VHN and 37 CF. The two groups were well matched for age, sex, prior period of starvation, diagnostic grouping, initial nutritional status, and duration of feeding (VHN, 13.1 days±8.72; CF, 14.6±12.14). There was no significant difference in the overall nitrogen balance, incidence of diarrhoea (VHN 24.2%; CF 28.5%), vomiting (VHN 27.3%; CF 25.1%), or mortality. In 15/18 (83.3%) cases of diarrhoea concurrent antibiotic or laxative therapy or injected feeds were implicated. Improvement in clinical, biochemical, and immunological parameters of nutritional status was similar in the two groups. Liver enzyme abnormalities occurred frequently (VHN 41.2%; CF 50%) but additional contributory factors could be implicated in 33% of these.

There is thus no evidence that elemental diets are superior to the cheaper and more palatable whole protein diets in malnourished patients with normal gastrointestinal function.

T41
Comparison of oligosaccharide and free glucose absorption from the normal human jejunum

B J M Jones, B E Brown, and D B A Silk (Department of Gastroenterology, Central Middlesex Hospital, London) During a recent infusion study net absorption of glucose from free glucose and from a partial hydrolysate of starch (Caloreen) was similar. Chromatographic data, however, suggested that, in the absence of luminal amylase, glucose uptake from polymers containing more than 10 glucose molecules was slower than from the monosaccharide, whereas uptake from lower molecular weight fractions was faster. The aim of this study was to determine whether the oligosaccharide end-products of starch digestion confer a kinetic advantage on glucose absorption.

Caloreen was incubated in vitro at 37°C with α-amylase to yield α-limit dextrins (12-5%), maltotetrose (1-7%), maltotriose (36-3%), and maltose (29-5%). The proximal jejunum of five normal subjects was perfused with three isotonic sugar-saline solutions containing (1) 140 mM glucose, (2) Caloreen, or (3) predigested Caloreen. Both Caloreen solutions yielded 140 mM glucose after complete hydrolysis. Glucose was absorbed at similar rates (mM per 25 cm/h±SEM) from free glucose (57±4.5±7) and Caloreen (61±8±3.9) but faster from predigested Caloreen (80-9±6.5, p<0.01) than from the free monosaccharide.

These findings indicate that the terminal products of luminal starch hydrolysis confer a kinetic advantage on glucose uptake implying that an advantageous relationship exists between the terminal products of luminal starch digestion, brush border hydrolysis sites, and the glucose transport mechanism.

T42
Comparison of the appearance of radio-labelled vitamin D3 and 25-hydroxyvitamin D3 in the chylomicron fraction of plasma after oral administration in man

J E Compston, A L Merrett, F G Hamnett, and P Magill (From the Gastrointestinal Research Unit, Rayne Institute, and the Department of Chemical Pathology and Metabolic Disorders, St Thomas’s Hospital, London) There is evidence that 25-hydroxyvitamin D (250HD) undergoes enterohepatic circulation; interruption of this circulation may be important in the pathogenesis of vitamin D deficiency in intestinal disease. However, little is known about absorption of 250HD in man; animal experiments indicate that, unlike vitamin D, it does not require bile acids and that only small amounts are bound to chylomicrons in plasma after absorption. We have compared uptake of orally administered 3H-vitamin D3 and 3H-250HD3 into plasma chylomicrons in nine healthy males.

Subjects received either 3H-vitamin D3 (6-25 μCi) or 3H-250HD3 (4 μCi) dissolved in ethanol, mixed with 1/45 pints of milk. Chylomicrons were separated from venous blood by ultracentrifugation. The mean percentage of total plasma radioactivity in the chylomicron fraction at two, three, four, and six hours after ingestion was 52.0, 33.0, 27.6, and 18.0 respectively after 3H-vitamin D3 and 9.1, 7.7, 5.9, and 5.9 after 3H-250HD3.

These results suggest that, in man, absorption of 250HD differs from that of vitamin D, possibly being less bile acid dependent. This would be compatible with its greater polarity and more rapid appearance in plasma after ingestion than vitamin D; it may also explain the effectiveness of oral vitamin D metabolites in patients with steatorrhoea.

T43
Effect of changing transit time on faecal bacterial mass in man

A M Stephen and J H Cummings (Dunn Clinical Nutrition Centre, Addenbrooke’s Hospital, Cambridge) Recent studies show that bacteria account for 60-70% of human faeces on a western diet. Excretion of bacterial mass varies among
individuals on identical diets, and is related to mean transit time through the gut.

To assess whether transit affects faecal output through changing bacterial mass, human volunteers took part in a metabolically controlled study. Subjects ate a diet high in fruit and vegetables (dietary fibre content 31 g/day) throughout. For three weeks, no treatment was given. Subjects then received either 3–4 tablets Senokot or 30–60 mg codeine phosphate and 0–8 mg Loperamide daily for an additional three weeks. Transit time was measured using the continuous marker technique and faecal bacteria by fractionation.

Senokot caused a significant reduction in transit from 64 hours to 35 hours (p < 0.025) (n = 6), resulting in increased faecal weight (147 g/day to 285 g/day, p < 0.005) and dry bacterial mass (16.5 g/day to 20.3 g/day, p < 0.025). With codeine, transit increased from 47 hours to 88 hours (p < 0.05) (n = 5) with resultant decreased faecal output (182 g/day to 119 g/day, p < 0.025) and bacteria (19.0 g/day to 16.1 g/day, p NS).

Bacterial mass and faecal output were closely related for all periods (r = 0.86, p < 0.001) (n = 19). A factor other than diet has been shown to affect colonic metabolism, alter bacterial mass and hence faecal output.

**T44**

Mechanism of faecal bulking by dietary fibre: a long-term study in patients with diverticular disease of the colon

M H ORNSTEIN, E R LITTLEWOOD, S BARTLETT, A G COX, AND I M BAIRD (Northwick Park Hospital, Harrow, West Middlesex Hospital, Isleworth) Fifty-eight patients with diverticular disease took part in a randomised, crossover, clinical trial. For 16 weeks each, they took three different regimens of dietary supplementation. The daily dietary fibre intake was increased from a mean (±SE) of 15 ± 1.6 g by 7.0 g during period A (predominantly bran crispbread), 9.0 g during period B (predominantly ispaghula), and 2.3 g during period C (refined wheat placebos).

Mean (±SE) daily faecal weights after each period were: wet weights—136 ± 6.4 g (A), 160 ± 7.9 g (B), and 118 ± 6.4 g (C); dry weights—29 ± 1.4 g (A), 28 ± 1.1 g (B), and 25 ± 1.3 g (C). Mean (±SE) stool total fibre contents were 52.8 ± 2.7 (A), 53.9 ± 2.4 (B), and 49.1 ± 2.2 (C) per 100 g dry weight, and of this 30.2% (A), 27.7% (B), and 33.0% (C) was cellulosic and 44.9% (A), 43.4% (B), and 39.9% (C) was non-cellulosic polysaccharides.

Stool water is increased with the two higher fibre supplements, but the difference from period C is far greater after period B (mean 39 ml, p < 0.001) than after period A (mean 14 ml, NS). Fibre content, however, is similar on all three regimens. These differences may be related to dose, but we believe they support recent short-term studies in normal volunteers taking far larger fibre supplements. These suggest that ispaghula is completely metabolised in the gut, but bran is not, and the stool bulking effect of ispaghula is due to the resulting increase in bacterial cell mass (which is 80% water). Bran produces its more modest effect largely by water-absorption. Work is in progress to confirm this using the method of faecal fractionation.

**T45**

Lactulose and bile: evidence linking colonic bacteria and cholesterol gallstones

J R THORNTON AND K W HEATON (University Department of Medicine, Bristol Royal Infirmary, Bristol) Cholesterol gallstone formation may be associated with increased colonic bacterial activity. Colonic bacteria degrade the primary bile acids (cholic and chenodeoxycholic acids) into secondary bile acids (deoxycholic and lithocholic acids) by 7a-dehydroxylation. Evidence suggests that this reaction is pH dependent and that it does not proceed below pH 6.5. Lactulose lowers colonic pH. To determine if reducing colonic pH affects bile composition, we have sampled duodenal bile from 10 healthy women before and after the administration of lactulose 30 ml tds for six weeks.

There was a consistent fall in the percentage of deoxycholic acid (28.4 ± 3.7 to 15.6 ± 2.4, p < 0.002). Conversely, chenodeoxycholic acid rose consistently (33.2 ± 3.2 to 42.9 ± 2.9%, p < 0.001). Cholic acid (36.0 ± 1.4 to 39.0 ± 1.8%) and lithocholic acid (2.5 ± 0.2 to 2.5 ± 0.2%) were not significantly changed. Concurrently, biliary cholesterol saturation index fell from 1.40 ± 0.11 to 1.19 ± 0.07, p < 0.005).

These data support the idea that colonic bacterial activity plays a part in the development of bile supersaturated with cholesterol and hence gallstone formation, and that these processes can be favourably influenced by lactulose. The effects of lactulose resemble those of wheat bran. Since bran is largely metabolised by colonic bacteria to fatty acids, reduction of colonic pH may be the mechanism of its action.

**T46**

Disordered transit of a meal through the small and large bowel in irritable bowel syndrome

N W READ (Clinical Research Unit, Royal Hallamshire Hospital, Sheffield) It is suspected that patients with irritable bowel syndrome (IBS) have disordered intestinal motility resulting in a disturbance in the passage of food through the gut. The transit of a standard meal (baked beans, mashed potato, sausages, and pineapple custard) through the small intestine and colon has been measured in 15 patients with IBS previously screened to eliminate organic bowel disease. In 10 patients who complained of diarrhoea the mouth to caecum transit time (20 ± 0.4 h, mean ± SEM) and the whole gut transit time (15.5 ± 3.7 h) were significantly shorter than the corresponding results in normal volunteers (3.9 ± 0.4 h, 35.5 ± h). Transit times were significantly shorter even in diarrhoea patients who had normal stool weights (n = 7). Conversely, in five patients who complained of constipation, small intestinal (4.9 ± 0.3 h) and whole gut transit times (52 ± 15 h) were longer than normal. There was a significant correlation between small intestinal and whole gut transit times in patients with IBS but not in normal subjects. Two-day stool weight was inversely correlated with whole gut transit time in normal subjects and patients with IBS, but correlated with small gut transit time only in the patients with IBS. Our results suggest that disordered small as well as large bowel transit plays a role in the pathogenesis of IBS.

**T47**

Where does the hydrogen come from in pneumatosis coli?

N W READ (Clinical Research Unit, Royal Hallamshire Hospital, Sheffield) Hydrogen in man emanates from bacterial fermentation of carbohydrate. In pneumatosis coli fasting breath hydrogen excretion is abnormally high. Two patients with numerous gas-filled cysts
in the left colon were studied. Both were flatulent but constipated passing between 10 and 70 g of predominantly blood-stained mucus per day. Fasting breath hydrogen concentration was over 50 ppm (normal less than 20 ppm). Puncture of the cysts revealed hydrogen concentration (1–5%) higher than that in the colonic lumen, indicating gas production in the cysts. After colonic washouts, breath hydrogen fell to 5 ppm, indicating that it was released from exogenous rather than endogenous carbohydrate. Jejunal culture was sterile and nutritional screen did not suggest malabsorption. Radiographs of the small bowel were normal. Transit of a standard meal through the small intestine was extremely rapid (less than 30 minutes; normal = 3±9±0±4 h, n = 17), while colonic transit was extremely slow. These results suggest that the high fasting levels of breath hydrogen result from bacterial fermentation of large amounts of unabsorbed carbohydrate entering the colon because of excessively rapid small intestinal transit. Submucosal cysts may result from abnormal mucosal permeability, allowing both bacteria and substrate to enter the submucosa.

T48
Is the gut an androgen target organ?

M J Farthing, G Wyatt, G Vinson, C R W Edwards, and A M Dawson (Departments of Gastroenterology and Endocrinology and The Medical College, St Bartholomew’s Hospital, London) A reversible abnormality with raised serum testosterone (T) and low serum dihydrotestosterone (DHT) occurs in coeliac disease. One explanation is that the gut is an important site for reduction of T to its active metabolite DHT, a conversion which is usually limited to androgen target organs. We have investigated this using homogenates, slices, and everted sacs of rat jejunum incubated with [3H] T and unlabelled T (4±0±10±4 M) and separated the metabolites by celite column, paper, and gas-liquid chromatography (GLC). Jejunal homogenates and slices oxidised T principally to androstenedione (A), a less potent androgen, with high conversions of up to 70%, depending on the substrate concentration. Jejunal slices in addition to androstenedione (32±0±1±5 pmol/mg wet weight/h) produced some reduced metabolites, one of which had the same elution profile on celite column and a retention time on GLC as DHT (10±1±1 pmol/mg wet weight/h). The major metabolites transported into the serosal media of everted gut sacs were DHT (1±3 pmol/100 mg wet weight/h) and the other reduced metabolites (1±9 pmol/100 mg wet weight/h). Experiments with germ-free animals have confirmed that these conversions are not due to bacteria. Thus the gut can oxidise T to androstenedione and reduce T to the more active metabolite, DHT. Testosterone stimulates cell proliferation in the small bowel and the above findings would suggest that its action may be mediated by DHT, the active metabolite found in androgen target organs.

T49
Immunocytochemical localisation of gut hormones in human fetal intestine

A M J Buchan, J M Polak, M G Bryant, and S R Bloom (Departments of Histochemistry and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) Although the diffuse neuroendocrine system is known to play a regulatory role in a number of gut functions, little is known about its development during fetal life.

The intestine (duodenum to colon) was collected from 33 fetuses ranging from 8 weeks old to full term. Samples were fixed for immunocytochemistry and stained by either the indirect immunofluorescence or peroxidase-antiperoxidase methods.

Gastrin-, somatostatin-, GIP- and motilin-containing cells were seen in the 8 week old fetuses; neurotensin-, entero-glucagon-, secretin- and CCK-containing cells and VIP-immunoreactive nerve fibres were detectable by 12 weeks of gestation. Met-enkephalin- and substance P-containing fibres were present by 16 weeks of gestation.

Quantitative studies showed an increase in cell number per mm² (c/mm²) in the maturing fetuses. In the duodenum, gastrin increased from 31 to 120 c/mm², motilin from 1 to 24 c/mm² and GIP from 3 to 24 c/mm².

In the youngest fetuses the gastrin and somatostatin cells were very numerous and there was an additional marked increase in gastrin cells before birth, suggesting that these peptides may be modulators of intestinal growth.

In conclusion: (1) the neuroendocrine system is well developed in early fetal intestine; (2) this development was completed by 25 weeks, which coincides with the earliest age of fetal viability.

T50
Effect of intestinal resection on entero-glucagon in rats

M Gregor, M G Bryant, A M J Buchan, S R Bloom, and J M Polak (Department of Medicine, Royal Postgraduate Medical School, London) After intestinal resection the mucosa of remaining gut shows compensatory hyperplastic transformation. This concept is widely accepted for absorptive epithelium but the effect on the endocrine intestinal organ is unknown. We have investigated the effects of increased intestinal resection length on entero-glucagon-containing L-cells of remaining gut and on basal plasma and tissue entero-glucagon concentrations. Five treatment groups were used (n = 8): control (no surgical procedure); sham-operated (transsection); 10, 50, and 90% distal gut resection. Six weeks after operation entero-glucagon concentrations were estimated by radioimmunoassay in plasma and remaining gut tissue.

Basal plasma entero-glucagon was significantly raised after 50 and 90% resection (controls 124±8 pmol/l; 50% 150±9, p < 0.05; 90% 163±7, p < 0.005). There was no significant difference in jejunal entero-glucagon concentrations between groups but ileal entero-glucagon was significantly increased after 50% resection (control 69±4; 50% 111±15 pmol/g, p < 0.02). This was more marked in the colon (control 93±14; 50% 163±15, p < 0.005; 90% 185±14, p < 0.001). L-cell number per single villus/crypt compartment, determined by immunocytochemical quantification, was unchanged in operated groups.

Conclusions: (1) After resection, the adaptational response of L-cells depends on increase in function rather than increase in number of functioning cells; (2) the observed increase of plasma and tissue entero-glucagon is consistent with its suggested role as a hormonal growth-promoting factor of absorptive mucosa.

T51
Abnormal retinal function in liver disease

W Ruse, P W N Keeiling, J O’Day, and R P H Thompson (Gastrointestinal Laboratory and Vision Research, St Thomas’ Hospital, London) Abnormality of dark adaptation has been
demonstrated in patients with alcoholic cirrhosis (AC) who had low plasma vitamin A levels. Most responded to vitamin A supplementation but a few required subsequent zinc supplementation or responded to zinc alone.

In nine patients (AC, six; active chronic hepatitis (ACH), three) total body zinc stores were assessed by leucocyte zinc content (LZC) and retinal function by electroretinography (ERG). None had visual symptoms or ocular abnormality. All patients with normal LZC (AC, four; ACH, one) had normal ERG. All patients with low LZC (AC, two; ACH, two) had abnormal ERG, with impaired b wave amplitude at 10 minutes (0.311 ± 0.033 v 0.116 ± 0.022 mV, mean ± SEM, normal LZC v low LZC, p < 0.005) and abnormality of photoreceptor function (red and white flicker fusion). Furthermore, b wave slope correlated with LZC (r = 0.783, p < 0.02, Spearman rank correlation coefficient). Serum vitamin A concentrations were measured in three of the four patients with low LZC and were normal.

These findings suggest that, in patients with liver disease and normal serum vitamin A levels, abnormalities of photoreceptor function may occur as a result of zinc deficiency alone, and that these abnormalities are not confined to AC.

Effect of bile on vitamin B₁₂ absorption

N H TEO, J M SCOTT, G NEALE, AND D G WEIR (Departments of Medicine and Biochemistry, Trinity College, Dublin, and Departments of Gastroenterology, Sir Patrick Dun's Hospital, and St James's Hospital, Dublin) Specific mechanisms for the absorption of vitamin B₁₂ and bile acids exist in the human ileum but their inter-relationship remains obscure. We have shown previously that bile acids both inhibit and dissociate intrinsic factor—vitamin B₁₂ complex and now report the effect of impaired flow of bile on the absorption of vitamin B₁₂ in both man and rat.

In normal human subjects mean absorption of vitamin B₁₂ was 21.4% (range 12–30%) (24 hours double-isotope Schilling test). Absorption was reduced in seven patients with obstructive jaundice (mean 12.3%; range 3–26.4%; four patients with values of <12%) and in seven patients with T tube drainage of the common bile duct after cholecystectomy for gallstones (mean 12%; range 5.7–22.4%; four patients with values of <12%). In four of the second group absorption improved after removal of the T tube (mean before 11.9%; range 6.5–22.4%; mean after 19%; range 9–31%).

In control rats the mean combined hepatic and renal uptake of ⁵⁷Co B₁₂ at seven hours after intragastric administration of 0.005 μg was 14.48 ± 5.8% in the rats with a ligated bile duct uptake was impaired (6.40 ± 1.78%) unless the ⁵⁷Co B₁₂ was given with rat bile (16.18 ± 0.80%) (mean ± SEM; n = 8; p < 0.001). These experiments suggest that bile acid deficiency may impair the absorption of vitamin B₁₂.

Vitamin B₁₂ absorption in the guinea-pig ileum

W J JENKINS, D P JEWELL, AND K B TAYLOR (Academic Department of Medicine, Royal Free Hospital, London) The mechanism of absorption of B₁₂ in the distal ileum remains a mystery. There is a significant delay between IF-B₁₂ binding at the brush-border and the appearance of B₁₂ in the portal blood. We have studied the change in the subcellular distribution of B₁₂ during its absorption across the ileal enterocyte.

Fasted guinea-pigs (six) were initially fed 10 ng ⁵⁷Co cyanocobalamin, and then 10 ng ⁵⁷Co cyanocobalamin at two hours. After killing the animals at four hours ileal homogenates were prepared in iso-osmotic buffered sucrose. Subcellular fractionation of post-nuclear preparations was carried out in iso-osmotic gradients of Percoll, and organelles in the fractions were identified by assaysing specific marker enzymes. The distributions of ⁵⁷Co and ⁴⁴Co cyanocobalamin were quite different. ⁴⁴Co cyanocobalamin given first was concentrated predominantly within the cytosol with smaller peaks in the brush-border and lysosomal fractions. In contrast the ⁴⁴Co cyanocobalamin given later was concentrated in the brush-border and lysosomal fractions only. These findings were consistent with B₁₂ absorption by receptor-mediated endocytosis. It is suggested that, after binding at the brush-border, B₁₂ is first sequestered within lysosomes, and then released into the cytosol, from where it leaves the cell to enter the portal blood.

Iron uptake by purified intestinal microvillus membranes

T M COX AND M W O’DONNELL (introduced by V S Chadwick) (Royal Postgraduate Medical School, London) The small intestine maintains iron balance by regulating absorption to meet body requirements. The localisation of the control step in the absorptive pathway is unknown, but recent studies showing accelerated iron uptake across the duodenal brush border in iron deficiency suggest that the initial entry process plays an important role.

In order to examine initial absorptive events in detail, microvillus membranes were purified from proximal rabbit intestine and incubated under physiological conditions with 45–450 μM ⁵⁹Fe ascorbate. Membrane radioactivity was separated by rapid microfiltration and was proportional to protein concentration. Time-dependent iron incorporation was observed for 60–90 minutes and exhibited saturation kinetics. At equilibrium, uptake was independent of osmotic gradients, indicating binding of iron rather than transport. Iron uptake by ileal membranes was 20–50% lower than by membranes from corresponding proximal intestine (p < 0.001).

At 90 μM medium concentration, iron uptake by membranes prepared from iron-deficient animals was increased—up to twofold—compared with membranes from matched controls (p < 0.001, n = 5). Moreover, kinetic studies revealed an increased Vmax (59.5 ± 8.1 versus 34.4 ± 3.6 natom Fe/min/mg protein, p < 0.01), without corresponding alterations in Km (approximately 130 μM), indicating increased numbers of iron-binding sites.

We suggest that net iron flux across the intestine is controlled at the initial uptake step by modulation of specific iron receptors on the luminal membrane.

Abstract No. T55 withdrawn

Immunoreactive prostanoids (PGs) of the E and F series, thromboxane B₂ (TXB₂) and 6-keto-PGF₁α in human jejunal fluid: characterisation and measurement

S COUTROT, F DRAY, AND C MATUCHANSKY (Service de Gastroentérologie, Université de Poitiers, and Unité de Radioimmunologie
Analytique, Institut Pasteur, Paris, France)

Very few data are available on the in vivo occurrence of PGs in human intestinal fluids. We have investigated if immuno-reactive PGs and related compounds were present in jejunal fluids from five controls and five patients with exocrine pancreatic insufficiency or jejunostomy. A slow-marker perfusion technique with a triple lumen tube (except in jejunostomised patients) was used during fasting and after a test meal. Specific radioimmunoassays of PGE₁, E₂, F₂α, TXB₂, and 6-keto-PGF₁α were performed on purified jejunal fluids, blood plasma, and test meals. Polyethylene glycol 6000 was used to separate bound from free iodinated or tritiated radioactivity; special techniques were raised to circumvent artefacts due to interference of jejunal fluid chemicals with antigen-antibody reaction.

Appreciable concentrations and outputs of 6-keto-PGF₁α were found in fasting intestinal contents of controls (582±208 pg/ml, and 458±128 pg/min respectively, M±SD); similar levels were observed in patients with no pancreatic enzymes and in non-intubated jejunostomised subjects. PGE₂, F₂α, and TXB₂ were also found, although in much lower concentrations. Fasting and postprandial outputs were not different. No PGE₁ was detected. We conclude that human jejunal fluid contains high levels of immuno-reactive 6-keto-PGF₁α, lower levels of PGE₂ and F₂α, but no PGE₁. Such a profile is quite different from that observed in human plasma.

Twenty-one normal subjects each drank a liquid meal of 200 ml water containing 20 g lactulose and 250 µc 99mTc-DTPA. Gastric half-emptying time (T½) was measured using gamma camera imaging; breath samples taken during and after the imaging were analysed for breath hydrogen content and the mouth to caecum intestinal transit time (TT) estimated.

Analysis of the data showed that there was no significant correlation (r=0.26, p>0.2) between T½ and TT, nor was the shape of the breath-hydrogen curve related to T½. There is, thus, no evidence that the rate of gastric emptying of liquid meals influences their subsequent small-intestinal transit.

This simple technique measures two parameters of gastrointestinal transit at one sitting, thereby allowing the study of their interrelationship. It should prove useful for the study of gastrointestinal transit in disease states.

P2 Cirrhosis and primary liver cell carcinoma in Tayside: a five year study

W S HISLOP, NORMA MASTERTON, I A D BOUCHIER, AND D HOPWOOD (Departments of Medicine and Pathology, Ninewells Hospital, Dundee) This study reviewed 197 cases of hepatic cirrhosis and 26 cases of primary liver cell cancer (PLCC) in Tayside between 1975 and 1979. Despite Scotland's well-known alcohol problem, there has previously been scant information on the aetiology of cirrhosis.

The survey was based on all histologically proven cases of cirrhosis and PLCC in the study period. There was a constant rate of presentation of cirrhosis of about 40 new cases per year, with a stable pattern of aetiology. About 55% of cases were due to alcohol, without a significant change in the proportion over the five year period. In alcoholic cirrhosis, no evidence for an increasing female susceptibility or earlier female morbidity was found. Cryptogenic cirrhosis, cardiac cirrhosis, and secondary biliary cirrhosis were more often diagnosed at necropsy. Bronchopneumonia, hepatic failure, gastrointestinal bleeding, and cardiac failure were the most frequent causes of death. Ninety-one per cent of cases of primary biliary cirrhosis were found in females, but the expected male preponderance in haemochromatosis was not present, about half the cases occurring in post-menopausal women.

Primary liver cell cancer had occurred in 5% of the cases of cirrhosis by the end of 1979.

P3 Non-specific esterases in gallbladder epithelium in cholecystitis

D HOPWOOD, E KOUROUMALIS, P E ROSS, AND I A D BOUCHIER (Departments of Medicine and Pathology, Ninewells Hospital and Medical School, Dundee) Neutral and acid non-specific esterases were demonstrated histochemically in the gallbladder epithelium of 112 patients with cholecystitis and in infiltrating macrophages of the lamina propria in cases with cholesterolosis.

These enzymes were studied in mucosal homogenates in four main groups of patients: cholesterol stones (89), pigment stones (13), acalculous cholecystitis (10), and cholesterolosis (eight).

Neutral esterase activity was significantly lower in the cholesterol stone group and significantly higher in acalculous cholecystitis, as compared with the pigment stone and cholesterolotic patients.

Acid esterase activity showed the same trends and there was a close linear correlation between neutral and acid esterase values in all cases (r=0.96, p<0.001). However, the two enzymes reacted differently to a wide range of inhibitors and activators. The main difference was that both tauro and glycocholate increased the activity of acid esterases, but inhibited neutral esterase activity.

Polycyclic amine gel isoenzyme patterns showed an extra band of slow-moving isoenzyme in all the cholesterol stone patients (47) and in only two of 23 of the rest.

The endogenous substrate for esterases is not known, but we conclude that these findings suggest an abnormality in lipid metabolism of gallbladder epithelium possibly related to gallstone formation.

P4 Gallbladder filling by isotope scanning: validation and application to gallstone patients

R M KUPFER, R P JAZRAWI, C E BRIDGES, AND T C NORTHFIELD (Departments of Medicine and Nuclear Medicine, St George's Hospital Medical School, London) Cholesterol gallstone patients have supersaturated fasting gallbladder bile. This could be due to increased gallbladder filling with fasting hepatic bile, which is
supersaturated with cholesterol even in healthy controls. We have, therefore, developed and validated a technique for measuring gallbladder filling after intravenous \(^{99}\)TcHIDA. Gallbladder activity was measured at 90 minutes, and expressed as percentage of gallbladder plus gut activity. We used two isoosensitive scanning heads at the front and back of the patient in order to cancel out errors due to differences in gallbladder depth, which depend on the inverse square law. In vitro validation studies with phantom gallbladder in a water bath (to mimic absorption of human tissues) gave maximum error of only 5% if two heads were used (compared with 300% with a single head). In vivo, errors due to differences in gallbladder depth were less than 8%, and duplicate studies gave mean difference of 10%. Gallbladder filling (mean ± SEM) was 54±8% in 16 patients with radiolucent gallstones, and compared with 57±8% in 16 controls. We conclude that radioisotope scanning using two isoosensitive heads provides a simple and valid method of assessing gallbladder filling; and that filling is not increased in gallbladder patients.

P5
Effect of artificial depletion of bile acid pool on hepatic and gallbladder bile in man
R P JAZRAWI, C BRIDGES, A JOSEPH, AND T C NORTHEFIELD (Departments of Medicine, Nuclear Medicine and Ultrasound, St George's Hospital Medical School, London) Cholesterol gallstone patients have reduced bile acid (BA) pool size and increased saturation index (SI) of fasting gallbladder (GB) bile. We have, therefore, examined whether artificial depletion of BA pool increases SI of fasting GB bile; and, if so, whether this is due to increased GB entry of basal hepatic bile (with high SI) and/or decreased entry of stimulated hepatic bile (with low SI). Eight volunteers without gallstones were studied fasting on two consecutive days. On day 1 BA pool was depleted by aspiration of bile-rich duodenal fluid. On both days we measured fasting GB volume (ultrasound), BA pool (isotope dilution), GB filling (cholecintigraphy), BA mass in BA (\(^{99}\)TcHIDA as recovery marker), and SI of basal hepatic bile and of GB and stimulated hepatic bile after cholecystokinin infusion. BA pool size fell from 8.2±0.9 to 6.4±0.9 mM (p<0.05). SI of fasting GB bile rose from 0.9±0.05 to 1.23±0.06 (p<0.05), but SI of basal and stimulated hepatic bile was unchanged. BA mass in GB fell from 4.9±0.05 to 3.8±0.5 mM (p<0.05), and GB volume from 35±4 to 20±2 ml (p>0.05), suggesting decreased entry of bile, but basal GB filling was unchanged. We conclude that artificial depletion of BA pool increased SI of fasting GB bile, probably by decreasing entry of stimulated hepatic bile.

P6
Vascular pattern of the omentum as basis for omental surgery
D LIEBERMANN-MEFFERT AND M ALLGÖWER (introduced by J Rhodes, Cardiff) (Department of Surgery, University Hospital, Kantonsspital, Basel/Switzerland)

The greater omentum is increasingly used by abdominal surgeons as a substitute for abdominal defects—for example, to fill spaces caused by exenteration and heavy irradiation of the pelvic floor, or after removal of echinococcus cysts in the liver. The omentum can be exteriorised and led to the body surface to cover defects of the chest wall.

In both procedures the omentum needs to be freed from the greater curvature of the stomach and this often deprives the stomach of its blood supply. Gastric dysfunction, distortion, and complaints may follow. In order to avoid these complications and find a more suitable approach we examined the vascular supply to the omentum and stomach arteriographically.

In contrast to earlier reports we found that the gastroepiploic vessels usually do not form a widely open arterial arcade or that a connection even is absent. This may be the reason for the complaints after omental surgery.

The vascular pattern found gives rise to a safer and more suitable lengthening method of the omentum. This method will be illustrated.

T57
Radio-opaque gallstones—reduction in size and calcium content on treatment with Rowachol
W R ELLIS, D H ROSE, C R RICHMOND, A Y NEHRU, ALIYA MIDDLETON, AND G D BELL (Departments of Therapeutics and Radiology, Nottingham City Hospital; Department of Biochemistry, Queen's Medical Centre, Nottingham and Wolfson Institute of Interfacial Technology, Nottingham).

The calcified moieties of radio-opaque gallstones fail to dissolve even on prolonged exposure to cholesterol-desaturated bile; consequently such stones are refractory to treatment with chenodeoxycholic and ursodeoxycholic acids. However, two radio- graphically documented reports record complete or partial disappearance of densely calcified stones during chronic (up to two years) ingestion of Rowachol. This preparation contains six monoterpenes including menthol, whose glucuronide enhances calcium solubility in vitro. Stimulated by these observations we have treated 14 patients with radio-opaque gallstones for periods of six to 18 months, using Rowachol.

Calcified rims appeared radiologically less distinct and/or complete in three patients after 12 (CG), 10 (FB), and 18 months, while stones were adjudged smaller or less opaque after treatment in three other cases. The surgically removed stones of CG and FB were examined by x-ray diffraction analysis (Dr June Sutor) and scanning electromicroscopy: apart from scattered small calcium-rich patches, the calcium content of the previously radio-opaque surface approximated to that of the (radiotranslucent) interior suggesting considerable dissolution of calcific material.

We conclude that further investigation into the potential role of terpenoid compounds in management of calcified gallstones appears to be warranted. We are currently screening pure terpene glucurono nides for activity in vitro.

T58
Best buy bile acid treatment for gallstones
D P MAUDGAL, R M KUPFER, R BIRD, AND T C NORTHEFIELD (Norman Tanner Gastroenterology Unit, St James's Hospital and Department of Medicine, St George's Hospital Medical School, London) The minimum effective dose, to give mean saturation index (SI) of 0.8, is lower for ursodeoxycholic acid (UDCA) than for chenodeoxycholic acid (CDCA), but dose/response studies have not been carried out with the two bile acids in the same patients. Bedtime administration of UDCA and low cholesterol diet enhances the effect of CDCA. We have, therefore, compared
the effect on SI in the same six gallstone patients of UDCA and CDCA, at meal-times with a normal cholesterol diet (conventional regimen), and at bedtime with low cholesterol diet. On all four regimens, each patient took three different doses of bile acid for one month each in random order. SI of fasting gallbladder bile was measured according to Hegardt and Dam without Carey correction factor.

Minimum effective dose from calculated regression lines was 17.3 and 15.0 mg kg \(^{-1}\) day \(^{-1}\) for CDCA and UDCA respectively on conventional regimen, and 10.1 and 9.8 mg kg \(^{-1}\) day \(^{-1}\) on bedtime administration plus low cholesterol diet. We conclude that any advantage of UDCA over CDCA is minimal when they are compared in the same patients; and that, as UDCA has to be synthesised from CDCA, the most cost-effective regimen is CDCA at bedtime with a low cholesterol diet.

T59
Prospective randomised trial of hydrocortisone foam versus conventional hydrocortisone enemas in distal colitis
R J DICKINSON, W S J RUDDELL, M F DIXON, AND A T R AXON (Gastroenterology Unit, General Infirmary at Leeds and Department of Pathology, University of Leeds) Steroid retention enemas are of proven value in the treatment of exacerbations of distal ulcerative colitis. Some patients experience difficulty in retaining conventional enemas and for this reason a foam-based product (Colifoam) has been advocated. Although the latter has attracted considerable attention, it has not been subjected to comparative studies and its therapeutic efficacy remains unproven. To test this we have conducted a trial comparing equivalent morning and night-time doses of intrarectal hydrocortisone given either in conventional form (as Cortenemas) or in a foam carrier (as Colifoam) assessing clinical efficacy and acceptability in patients in exacerbations of distal colitis. At the beginning and at the end of the trial the patients were assessed on the basis of their symptoms and by sigmoidoscopy with rectal biopsy. Thirty patients were included, 15 receiving either treatment. Treatment success was achieved in approximately 70% of the patients in either group but the foam was more easily retained and was preferred to conventional enemas by 11 of the 12 patients who, during a previous exacerbation, had received the latter.

Hydrocortisone foam is as efficacious as conventional enemas in the treatment of distal colitis and offers advantages in terms of patient preference and ease of retention.

T60
Prostaglandin synthesis inhibitors in active ulcerative colitis: flurbiprofen compared with conventional treatment
D S RAMPTON AND G E SLADEN (Gastroenterology Unit and Department of Medicine, Guy’s Hospital Medical School, London) It has been suggested that prostaglandins (PG) play a pathogenetic role in ulcerative colitis. We have therefore performed a one-week open trial to compare the effects of the PG synthesis inhibitor, flurbiprofen (50 mg orally qds), with those of conventional treatment with topical corticosteroids and oral sulphasalazine, in two groups of seven patients with active ulcerative colitis. Conventional treatment tended to improve stool frequency, rectal bleeding, and sigmoidoscopic appearance. Rectal mucosal PGE \(_2\) release, measured by in vivo rectal dialysis, fell from 1072 ± 253 pg cm \(^{-2}\) h \(^{-1}\) (mean ± SEM) before, to 599 ± 203 pg cm \(^{-2}\) h \(^{-1}\) (p < 0.05) after one week of conventional therapy; rectal mucosal potential difference rose from -28 ± 5 to -40 ± 5 mV (p < 0.05), and sodium absorption from 59 ± 14 to 81 ± 17 mmol cm \(^{-2}\) h \(^{-1}\) (p < 0.05). In contrast, despite a similar fall in mucosal PGE \(_2\) release (1323 ± 218 to 895 ± 181 pg cm \(^{-2}\) h \(^{-1}\), patients given flurbiprofen showed no clinical improvement; indeed, deteriorations in rectal potential difference (-29 ± 5 to 21 ± 6 mV, p < 0.05) and sodium absorption (73 ± 12 to 41 ± 12 mmol cm \(^{-2}\) h \(^{-1}\), p < 0.05) occurred. Furthermore, flurbiprofen-treated patients fared significantly worse than those on conventional treatment in respect of rectal bleeding (p = 0.05), sigmoidoscopic appearance (p = 0.01), rectal potential difference (p = 0.01) and sodium absorption (p = 0.01).

These results do not support the hypothesis that increased mucosal PG production is of major pathogenetic importance in ulcerative colitis, and suggest that flurbiprofen and other PG synthesis inhibitors are unlikely to prove useful alternatives to conventional treatment.

T61
Sulphasalazine and male infertility
S TOOVEY, A J LEVI, AND W F HENDRY (Department of Gastroenterology, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex and Fertility Clinic, Chelsea Hospital for Women, London) The semen of 18 patients on chronic sulphasalazine therapy for inflammatory bowel disease was examined. Eight had complained of infertility. Density was below normal (≥ 40 x 10\(^6\) spermatozoa. ml \(^{-1}\)) in 15/17 examined, motility below normal (≥ 60% progressively motile spermatozoa) in 18/18 examined, and morphology disturbed in 10/16 examined (normal < 30% abnormal forms). No significant differences were evident in these three semen qualities between patients complaining of infertility and those not (Mann-Whitney). In nine patients semen was re-examined at least two months after sulphasalazine withdrawal: density and motility had improved significantly (p = 0.01 and p = 0.025 respectively, Wilcoxon). Morphology remained unchanged. The time course of the improved semen quality after sulphasalazine withdrawal will be shown. Ten pregnancies were fathered by eight patients after sulphasalazine withdrawal: six of these had complained of infertility. Five of the 10 pregnancies resulted in normal infants, one miscarried, and four are still less than term. These findings confirm and extend our earlier observations. Data will be shown on possible mechanism for this important and common side-effect of sulphasalazine.

T62
Sulphasalazine and male fertility
J G FREEMAN, V A C REECE, AND C W VENABLES (Department of Surgery, Royal Victoria Infirmary, Newcastle upon Tyne) Sulphasalazine is widely used in the maintenance treatment of inflammatory bowel disease. Male infertility is not a recognised side-effect of sulphasalazine treatment, although several isolated cases have been documented. We have examined the semen from males with no history of infertility and who attend an inflammatory bowel clinic. They were divided into those who took sulphasalazine (n = 10) and those whose bowel disease did not require sulphasalazine (n = 6). Semen analysis included sperm...
Oligospermia associated with sulphasalazine therapy

G G BIRNIE, T MCLEOD, AND G WATKINSON (Departments of Gastroenterology and Pathology, Western Infirmary, Glasgow)

The association of oligospermia and sulphasalazine therapy in patients attending for infertility investigation has been noticed.

Twenty-three young men with inflammatory bowel disease were interviewed who had received maintenance treatment with sulphasalazine for a mean period of 3-7 years, range two months to 10 years. Their average age was 32-9 years, three were single and the 20 married men had fathered in all 29 children, an average of 1.45 per married man. Only three children were born while the father was receiving sulphasalazine.

Twenty-one patients were able to produce sperm samples, four (19%) showed normal sperm counts exceeding 60 million per cu mm, seven (33%) had low counts varying between 20-60 million, while 10 (48%) were frankly oligospermic with counts below 20 million per cu mm. Thirty-eight per cent of the spermatozoa examined exhibited abnormalities in morphology, while the average motility was low with 37% of sperm being mobile at one hour.

In three patients in whom it was possible to withdraw sulphasalazine there was a prompt return to normal sperm counts, morphology, and motility.

The findings confirm that subfertility is a common finding in young men receiving sulphasalazine for inflammatory bowel disease; and subfertility can in some cases be reversed by withdrawing the drug.

Effects of mepenzolate bromide on colonic motility and symptoms in patients with refractory Irritable bowel syndrome

R A MOUNTFORD, R F HARVEY, AND A E READ (University Department of Medicine, Bristol Royal Infirmary, Bristol)

Although many patients with the irritable bowel syndrome respond well to reassurance and treatment with a high fibre diet, many do not. Only a few drugs are available which modify the abnormal colonic motor activity which is believed to cause many of the symptoms experienced by such patients, and, in most cases, the effects of these drugs on the colon have not been fully tested.

The effects of a single dose of mepenzolate bromide (50 mg orally) on colonic motor activity were studied in a double-blind crossover trial in 22 patients with the irritable bowel syndrome whose symptoms had not responded to conventional treatment. Sigmoid motor activity was measured, both fasting and after a standard meal, using miniature air-filled balloons connected to transducers.

Fasting colonic motor activity was significantly decreased by the active drug (mean percentage activity 34.9 to 14.5%, p<0.01, motility index 66.3 to 68.6, p<0.01). A similar decrease was seen after the meal (percentage activity 33.9 to 16.75%, p<0.01, motility index 148.8 to 74.4, p<0.01). Symptoms were reduced more in the fasting state than after the meal. No side-effects were observed.

We conclude that mepenzoate bromide markedly decreases colonic motor activity, and thus should be a useful treatment for patients with refractory irritable bowel syndrome.

Comparison of treatments for the irritable bowel syndrome (IBS)

J A RITCHIE AND S C TRUELOVE (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford)

A previous therapeutic trial of factorial design indicated that a combination of therapeutic agents, lorazepam, hyoscine hydrobromide, and ispaghula husk relieved symptoms of IBS more effectively than those agents given singly. Another trial of similar design has been undertaken to compare these three agents with others having equivalent clinical actions — namely, Motival (fluphenazine/nortriptiline mixture), mebeverine, and bran.

Ninety-six patients took part; all received three agents, one from each pair being compared, in all possible combinations.

Fifty-six patients reported a sustained symptomatic improvement, significantly more than in the previous trial when placebos were used. Ispaghula was significantly more effective than bran. The combination including ispaghula, Motival, and mebeverine improved 11 out of 12 patients, significantly more than bran, Motival, and hyoscine (five improved) or bran, lorazepam, and mebeverine (four improved). Mebeverine with either bulking agent was significantly more effective when combined with Motival (18 out of 24 improved) than with lorazepam (10 improved).

These results confirm the value of a combined therapeutic approach to the relief of IBS and suggest the possibility of synergism between agents. The choice of those which are to be combined is evidently of crucial importance and indicates the need for further systemic studies of therapy in IBS.

Early morning retching—hernia gastro-pathy syndrome

H A SHEPHERD, D COLIN-JONES, J HARVEY, AND A JACKSON (Queen Alexandra Hospital, Cosham, Portsmouth, Hants)

Vomiting complicated by haematemesis from mucosal trauma was described by Mallory and Weiss. Axon et al. (1975) and Young et al. (1976) described similar cases in whom early endoscopy revealed pathology other than the expected tear. This was confirmed by Thomas et al. (1979) who reported endoscopic observations in alcohol abusers suggesting that
repeated retching could cause gastric mucosa to prolapse into the oesophagus with resultant trauma and haematemesis.

We describe the clinical syndrome of 18 patients (mean age 34 years), often smokers, less often drinkers, who present with attacks of epigastric pain associated with early morning (50%) or postprandial (44%) retching. Haematemesis may occur (39%) but more often vomitus is scanty, even when postprandial. The patients all display a sensitive gag reflex and often a bruised uvula.

Endoscopy confirms their tendency to retch, and their ability to herniate a knuckle of macroscopically abnormal gastric mucosa into the oesophagus. Biopsy may demonstrate mucosal haemorrhage and oedema (50%).

Avery Jones refers to anxious patients who experience bouts of early morning sickness provoked by coughing; we suggest that our patients with epigastric pain reflect this presentation demonstrating a hitherto poorly recognised syndrome—hernia gastropathy. We propose that its early recognition may obviate the need for further gastrointestinal investigation. Detailed clinical features will be presented.

T67
Comparison of capsule and duodenoscopic biopsy specimens in the diagnosis of small intestinal disease

A S ME, M BURKE, J NEWMAN, AND P B COTTON (Gastrointestinal Unit and Bland Sutton Institute of Pathology, The Middlesex Hospital, London) Duodenoscopic biopsy is becoming increasingly popular for the diagnosis of small bowel disease but its accuracy in comparison with standard capsule methods is unknown. Using an Olympus GIFQ fibroscope and an oversleeve, we have been able to take four different types of specimen from each of 25 patients at a single session: Crosby capsule biopsies from the jejunum and the distal duodenum and forceps biopsies using both paediatric and standard forceps (four specimens with each).

All biopsies were coded, assessed blind, and graded according to strict criteria.

Specimens adequate for diagnostic assessment were achieved in 25 patients (100%) by standard forceps, 24 patients (96%) by paediatric forceps, 20 patients (80%) by jejunal capsule, and 14 patients (58%) by duodenal capsule.

Seven patients had villous atrophy. Paediatric forceps biopsies failed to make the diagnosis in one and duodenal Crosby capsule biopsy in two.

Duodenoscopic biopsy using standard forceps is the most reliable method for diagnosing small intestinal villous abnormality, although four specimens must be taken to provide at least one that is adequate for diagnosis.

T68
Intestinal permeability in coeliac disease: effect of gluten withdrawal and single dose gluten challenge

I HAMILTON, I COBDEN, J ROTHWELL, AND A T R AXON (Gastroenterology Unit, The General Infirmary at Leeds) The use of a hypertonic solution containing mannitol and cellobiose as probe molecules to demonstrate abnormal intestinal permeability in coeliac disease has been described. We report the effect of gluten withdrawal and subsequent challenge on intestinal permeability measured by this technique.

Of 21 patients with coeliac disease, all had abnormal cellobiose/mannitol absorption ratios before treatment. After at least three months' gluten withdrawal, 20 had values within the normal range (p < 0.002). Ten patients were studied at regular intervals after gluten withdrawal. Nine showed gradual return of permeability to normal over the first three months, and remained normal excepting probable dietary indiscretion. Patients with lymphoma and Crohn's jejunitis remained abnormal.

Six coeliac patients were studied before and daily for five days after a single dose of 30 g gluten. In each case results became clearly abnormal within four days, with maximum mean abnormality on day 3 (p = < 0.05). All returned to normal by day 5 (p = < 0.05). Control subjects remained normal throughout.

We conclude that this technique provides a reliable way to monitor treatment in coeliac disease, and a quick non-invasive means of demonstrating gluten sensitivity. There is a mean delay of four days between ingestion of gluten and maximal effect on intestinal permeability.

T69
Initial evaluation of a single-day tubeless pancreatic function test

C J MITCHELL, F G SIMPSON, J KELLEHER, AND M S LOSOWSKY (Department of Medicine, St James's University Hospital, Leeds) Urinary recovery of p-aminobenzoic acid (PABA) produced by the chymotrypsin hydrolysis of orally administered N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BTP) provides an indirect index of pancreatic exocrine function. We have previously shown that the misleadingly abnormal results occurring in patients with malabsorption can be eliminated if a second absorption test is performed using oral free PABA to derive a PABA Excretion Index (PEI) as the ratio of PABA recoveries from oral BTP and free PABA. To produce a single-day test, BTP (2g) with 14C-PABA (5μCi) was given to 25 subjects and the urinary six hours chemical and isotopic PABA recoveries were measured simultaneously to derive the PEI.

In 10 normal subjects the PEI range was 0.72–0.96 and significantly higher (p < 0.001) than in eight chronic pancreatitis patients (PEI range 0.47–0.73). In seven patients with small bowel disease and malabsorption without evidence of pancreatic disease the PEI (range 0.76–1.32) was similar to normal subjects and distinguished these patients from those with pancreatitis, even though PABA recovery from BTP alone was abnormally low.

These results suggest that this test can reliably assess pancreatic exocrine from a single six hour urine collection without requiring duodenal intubation.

T70
Oral pancreatic function test (PFT) in acute pancreatitis

C J MITCHELL, M J PLAYFORTH, J KELLEHER, AND M J MCMAHON (Department of Medicine, St James's University Hospital, Leeds, and Department of Surgery, The General Infirmary at Leeds) The diagnosis of acute pancreatitis (AP) is difficult after serum amylase levels have returned to normal, but pancreatic exocrine function remains impaired for a longer time. The oral PFT using N-benzoyl-L-tyrosyl-p-aminobenzoic acid assesses exocrine function from urinary recovery of p-aminobenzoic acid (PABA) produced by chymotrypsin hydrolysis of the peptide. This test was performed in 30 patients with established AP within two weeks of admission but after amylase levels had become normal and the results compared with 10 patients with non-pancreatic
abdominal pain and 10 subjects tested two years after recovery from AP.

All 30 patients with AP had an abnormal eight-hour urinary PABA recovery (range 7.5-55%; normal >57%) that was most impaired in patients with idiopathic AP. PABA recovery was normal in all subjects recovered from AP (range 58-80%) and all patients with non-pancreatic abdominal pain (range 59-78%). Follow-up tests in 15 AP patients became normal in eight patients or improved in four patients by three to 12 months, but three patients showed progressively abnormal tests.

These results suggest that the oral PFT is useful in the diagnosis of AP when amylase levels have returned to normal and can provide a simple method of monitoring the subsequent course of the disease.

T71
SeHCAT can detect ileal malfunction

H NYHLIN, M V MERRICK, AND M A EASTWOOD (GI Unit and Department of Nuclear Medicine, Western General Hospital, Edinburgh) SeHCAT is the taurine conjugate of a synthetic bile acid 23 selena 25 homocholic acid. The metabolism of the compound is in many respects similar to that of natural conjugated bile acids. It differs in being resistant to bacterial deconjugation and dehydroxylation. Because SeHCAT is labelled with a gamma emitting radioisotope, $^{75}$Se, it can be measured using a whole body counter.

We have administered SeHCAT to 10 normal volunteers and to 40 patients with Crohn's disease, jejunoileal bypasses, or ulcerative colitis to ascertain whether it can be used to detect the presence of ileal disease, or to estimate its extent.

Whole body retention was measured four days and seven days after the administration of 1 $\mu$C. Normal subjects retained more than 15% of the administered activity at seven days. Ileal resection or ileal bypass retained less than 2%.

Patients with Crohn's disease involving the terminal ileum retained less than 10%; in those subjects without involvement of the terminal ileum and in those with ulcerative colitis the retention was within the normal range.

We conclude that SeHCAT can be used to detect malfunction of the terminal ileum and may give some indication of the severity of involvement.

T72
Does occult rectal bleeding predict relapse in ulcerative colitis?

I F TROTMAN, S CAMPBELL, AND S C TRUELOVE (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford) Fifty-six patients with ulcerative colitis in complete clinical remission for more than one month and taking no medication other than maintenance sulphasalazine volunteered to test their faeces regularly for occult blood using Fecatest, a modern guaiac test. After an initial period of instruction they performed two tests per week and were followed-up for six months or until they relapsed.

Twenty-two patients had persistently negative tests and all remained in complete clinical remission. Seven patients relapsed and all had shown positive tests for occult bleeding at least once week before the onset of symptoms. Ten other patients who remained in clinical remission also recorded one or more positive tests but the frequency of positive results in this group was significantly less than in those who relapsed ($p < 0.01$).

It is concluded that occult bleeding predicts relapse in patients with ulcerative colitis and also identifies a subgroup of patients with an increased risk of relapse.

T73
Air introduced per rectum can be used to give radiological contrast in severe acute colitis: the 'air enema'

D PRESTON, C J BARTRAM, B M THOMAS, AND J E LENNARD-JONES (St Mark's Hospital, London) The severity of acute colitis depends on the extent of inflammation and the depth of ulceration. In many patients a plain abdominal radiograph gives information about these variables because the colonic lumen and the mucosal outline are outlined by gas. In other patients little or no gas is present in the colonic lumen, though extensive and severe disease may be present. A barium enema can be performed without bowel preparation but is not usually undertaken in patients who are severely ill.

In 10 patients with acute colitis whose plain abdominal radiograph showed little or no gas in the colon about 750 ml of air was introduced per rectum and a second radiograph performed. The findings have been correlated with an unprepared barium enema performed on the next day. The 'air enema' satisfactorily defined the extent of disease, though only the barium enema showed the depth of ulceration. No complications occurred and patients preferred the introduction of air to the barium enema as it caused less discomfort. The 'air enema' may have a role in the initial assessment of those patients with severe acute colitis whose plain abdominal radiograph shows no gas in the colon.

T74
A logical description of the 'irritable bowel syndrome'

G P CREAN, W I CARD, R W LUCAS, AND D SPIEGELHALTER (Gastrointestinal Centre and Diagnostic Methodology Research Unit, Southern General Hospital, Glasgow) Some diseases can be defined by a single defining characteristic but others, such as the 'irritable bowel syndrome' (IBS) can only be described by some combination of a set of characters—that is, symptoms, signs, etc. Presumably such a combination is developed by the individual doctor implicitly but it could be made explicit by means of the Boolean algebra to form a rigorous logical description. If each character is either present or absent, if any two characters can be logically connected with an 'and' or an 'or', then, with certain reservations, the disease can be described by a Boolean function and displayed as a set of expressions where each expression contains each character as present or absent. This set is unique and describes the only ways in which IBS can present.

Five gastroenterologists examined independently more than 100 records of the presumed disease, each record containing the presence or absence of 20 characters. Their consensus judgement supplied the set of expressions which was used to form its logical description. Such a method, which has general application, could provide an agreed description of IBS and, for a computer program, a definition, whereby a diagnosis could be made by logical implication.

T75
Ultrasound of the gallbladder: experience in a district hospital

T M WALKER (introduced by R G FABER) (Royal Berkshire Hospital, Reading, Berkshire) The accuracy of ultrasound in the diagnosis of gallstones is widely accepted.
Most reports are from teaching centres where staff are experienced in ultrasound technique. In district hospitals staff often have had no formal training in ultrasound. Can similar results be obtained in these circumstances?

Results are presented from a district hospital for the first year after installation of a B-mode scanner. Two radiologists had no previous training in ultrasound, and three had only limited experience. Three hundred and sixty seven patients with suspected gallstones were scanned, mostly after unsuccessful or equivocal oral cholecystography. Operative confirmation of the ultrasound is available in over a third of the patients. In 83% of the surgical cases ultrasound was correct; the examination was inconclusive in 10% and incorrect in 8%. In 10 cases the gallbladder area was not visualised because of obesity or intestinal gas. In half of the incorrect cases more than six months elapsed between ultrasound and surgery.

These results are not as good as some recent reports from teaching centres, but the accuracy is remarkably high considering the lack of experience of the staff. In future it is to be expected that a greater accuracy will be achieved.

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IMMUNOLOGY
T76-T84

T76
Treatment of HBsAg positive chronic liver disease with Bacillus Calmette Guerin (BCG)

M F BASSENDINE, I V D WELLS, A MURRAY, J SUMMERS, H C THOMAS, AND S SHERLOCK (Department of Medicine, Royal Free Hospital, London, and The Institute for Cancer Research, Fox Chase, Philadelphia, Pennsylvania, USA) A study has been undertaken to determine the effectiveness of BCG immunotherapy in nine patients with HBsAg positive chronic active liver disease. BCG vaccine (Glaxo) was administered intradermally in 0.1 ml aliquots containing 0.03 mg dry weight of mycobacteria to a total dose of 0.3 mg, over a period of between 10 and 20 weeks. Subsequent follow-up was for at least three months.

In two of five patients with raised serum hepatitis B virus (HBV) specific DNA polymerase (DNAP) activity, BCG produced a gradual and sustained fall in DNAP to negative values, accompanied by a fall in serum levels of HBV-DNA (measured by hybridisation to cloned 32P-HBV-DNA), a fall in HBsAg concentrations (quantified by rocket immuno-electrophoresis) and a transient rise in aspartate transaminase.

In one of four patients with negative HBV-DNA, BCG was followed by the loss of serum HBsAg (RIA) and appearance of HBs antibody. Delayed-type (cell-mediated) hypersensitivity skin reactions were intensified by BCG administration in all nine patients. Therapy was well tolerated with mainly local side-effects.

In conclusion, immunotherapy with BCG was effective in three out of nine patients, with total clearance of HBV antigens (one) or decreased viral replication (two), accompanied by decreased inflammatory activity. It is now being evaluated as an adjuvant to antiviral therapy in a controlled trial.

T77
Circulating immune complexes in coeliac disease

A W BULLEN, R N MAINI, AND M S LOSOWSKY (Department of Medicine, St James's University Hospital, Leeds, and The Mathilda and Terence Kennedy Institute of Rheumatology, London) Circulating immune complexes have previously been detected in 100% of treated coeliac patients using three methods. It has been suggested that the complexes may either cause, or result from, damage to the small intestine and reticuloendothelial system. However, a later study found raised complex levels in only 24% of treated coeliaics, and the results were not significantly different from controls. In view of the discrepancy of published results, we report our findings using the Clq binding assay. We have related immune complex levels to treatment with a gluten-free diet (as an indicator of small intestinal damage), and hyposplenism (as an indicator of reticuloendothelial damage).

Raised immune complex levels were found in four out of 18 untreated patients (22%) and two out of 29 treated patients (7%). Levels in untreated patients were significantly higher than in treated patients (p < 0.05). There was no significant difference between patients with and without hyposplenism. In individual patients, there was no consistent effect after starting a gluten-free diet, and no correlation with C3 hypocomplementaemia.

The results suggest that the incidence of raised levels of circulating complexes, as measured by Clq binding activity, is considerably lower than previously reported, and support the view that such complexes are unlikely to be important in pathogenesis.

T78
Suppressor T-cells in human intestinal mucosa

W S SELBY, G JANOSY, G GOLDSTEIN, AND D P JEWELL (Royal Free Hospital, London) T-lymphocytes may be found in the epithelium and lamina propria of the human small and large bowel. To study this population, sections of normal intestine have been analysed by immuno-fluorescence, using antisera to T-lymphocyte antigen (HuTLA), suppressor-cytotoxic T-cells (OKT8-SUP), la-like (p 28, 33) antigens, and antibody to HLA-ABC core (W6/32). In small and large intestine, 70 to 90% of intraepithelial T-lymphocytes were of suppressor-cytotoxic phenotype (OKT8+). In contrast, 25 to 55% of lamina propria T-cells were OKT8+.

The epithelium was strongly HLA-ABC positive, but expressed la-like antigens only weakly. In the lamina propria, macrophages were strongly positive for la-like antigens. The differential expression of la-like and HLA-ABC antigens may determine the proportions of suppressor and non-suppressor T-cells in the epithelium and lamina propria. This in turn is likely to have functional significance within the multilayered immune defence of the gut.

T79
Suppressor cells in splenectomised and coeliac patients

D A F ROBERTSON, A W BULLEN, AND M S LOSOWSKY (Department of Medicine, St James's University Hospital, Leeds) In the regulation of the immune response, the spleen is important as a source of suppressor cells. Hyposplenism is common in coeliac disease. HLA status, particularly the B8 gene, may determine the degree of immune responsiveness to various stimuli.

Further to investigate these phenomena, suppressor cell activity was measured by pre-incubation of lympho-
cytes for 24 hours before stimulation with concanavalin A, and expressed as an index which, if low, implies impaired suppressor cell activity.

Four groups were studied: (1) 12 patients after splenectomy for trauma, (2) 12 treated coeliacs with hyposplenism, defined by impaired reticuloendothelial function, (3) 13 treated coeliacs without hyposplenism, and (4) 25 controls. The suppressor index in the splenectomised group (1.54±0.22) (mean±1 sem) and in all of the coeliacs (2.01±0.23) is significantly lower than controls (2.55±0.21) (p<0.01 and p<0.05 respectively). Surprisingly, there is no difference between hyposplenic coeliacs (2.05±0.25) and those without hyposplenism (1.98±0.39).

In the coeliac patients there is a significant (p<0.05) association between a low suppressor index and the presence of HLA B8.

These data demonstrate that the spleen is important in the normal suppression of the immune response and show, for the first time, impaired suppressor function in coeliac disease. This is related to the B8 gene but not, apparently, to splenic function as measured. Perhaps in coeliac disease suppressor function is lost even when other splenic functions are retained.

T80 Gladin antibodies in coeliac patients using the MrsPAH test

MARIANNE KIEFFER, P J CICLITIRA, J O HUNTER, AND R R A COOMBS (Division of Immunology, Department of Pathology, University of Cambridge, Addenbrooke's Hospital, Cambridge, and Department of Medical Gastroenterology, Addenbrooke's Hospital, Cambridge) Mixed Reverse (solid phase) Passive Antiglobulin Haemagglutination (MrsPAH), was used to measure IgG, IgA, and IgM antibody levels to gliadin in adults with coeliac or inflammatory bowel disease and in healthy control subjects.

Gliadin dissolved in alcohol was fixed onto the wells of plastic microtitre plates and serial dilutions of serum were added. After incubation and washing, red blood cells coupled with class-specific anti-human immunoglobulin were added to visualise antibodies bound to the antigen.

Twenty healthy control persons had IgG antibody titres (range and median) of 4–128 (16) and IgA antibody titres of 0–8 (0). Thirty-three patients with coeliac disease were studied. Twelve on a normal diet had IgG titres of 128–1,600 (1024) and IgA titres of 16–2048 (64). Twenty-one patients on a prescribed gluten-free diet had IgG titres of 32–4096 (512) and IgA titres of 0–128 (four). Twenty-two patients with Crohn's disease or ulcerative colitis had IgG titres of 16–512 (64) and IgA titres of 0–256 (four). IgM titres were generally low, though clearly highest in coeliacs on normal diet.

MrsPAH may become a useful diagnostic aid in coeliac disease and might also be used to monitor compliance with diet.

T81 Small intestinal IgE-cells in human giardiasis

J GILLON, C ANDRE, L DESCOS, AND Y MINAIRE (INSERM U45, Hopital Edouard Herriot, Lyon, France and the Gastrointestinal Unit and Wolfson Laboratory, Western General Hospital, Edinburgh) The immune response to infection with Giardia lamblia probably involves local and systemic antibody production as well as a local T-cell response. No studies of small-intestinal IgE-cells have been reported, but reports of an association with urticaria and bronchial asthma suggest that type 1 hypersensitivity may be provoked by this parasite. Using direct immunofluorescence we have measured total and class-specific immunoglobulin-containing cells in small-intestinal biopsies of 18 patients with untreated giardiasis, nine of these patients after treatment with metronidazole, and 25 controls—that is, normal biopsies from patients without giardiasis. There was no difference between total numbers of IgE-cells in patients before and after treatment and control subjects. However, the proportion of IgA-cells was significantly decreased (54%±3.0) in patients before treatment as compared with controls (73.5%±1.8, p<0.001), and the proportion of IgE-cells was significantly increased (13%±1.3, controls 2%±0.3, p<0.001). After treatment total numbers of IgE-cells remained constant, but IgA-cell numbers reverted to normal and the IgE-cell population decreased significantly to 3%±0.6 (p<0.001). These results suggest the presence of type 1 hypersensitivity in response to Giardia infection.

T82 Reversal by cyclophosphamide of orally induced tolerance to a protein antigen

A M MOWAT AND A FERGUSON (Gastro-Intestinal Unit, Western General Hospital and University of Edinburgh, Edinburgh) Feeding of a protein antigen to adult mice may induce both a secondary antibody response, and a state of unresponsiveness to subsequent systemic immunisation with the fed antigen—that is, tolerance. A single intragastric dose of ovalbumin reduces cell mediated immunity (CMI), as measured by skin test to 10% control, as well as suppressing antibody responses.

Recently, evidence has accumulated that this tolerance is due to induction of suppressor cells in the gut-associated lymphoid tissues. Cyclophosphamide inhibits suppressor cell activity in other systems, and we have therefore attempted to reverse orally induced tolerance by pre-treating animals with cyclophosphamide. This regime abolished orally induced suppression of the antibody responses, and induced partial reversal of the suppressed cell mediated immune response.

Cyclophosphamide pre-treatment, oral immunisation, and oral challenge with ovalbumin have also been used to induce a local intestinal CMI reaction. Migration inhibition tests with mesenteric lymph node cells showed the presence of sensitised lymphocytes, and crypt hyperplasia and intraepithelial lymphocyte infiltrate in the mucosa provided circumstantial evidence of a mucosal CMI reaction. Abrogation of the normal gut-associated suppressor mechanisms may be responsible for induction of many mucosal hypersensitivity reactions.

T83 HLA-D related antigens in inflammatory bowel disease

W R BURNHAM, K GELSTHORPE, M J S LANGMAN, A S PENA, J J VAN ROOD, AND I T WETERMAN (Academisch Ziekenhuis Leiden, Regional Blood Transfusion Service, Sheffield, and University Department of Therapeutics, Nottingham) Ten HLA-D related (HLA-DR) antigens were examined in 205 patients with inflammatory bowel disease and 648 normal controls.

One hundred and thirty-one of the patients had Crohn's disease and 74 ulcerative colitis.

Only 47 patients with inflammatory bowel disease had Crohn's disease and 74 ulcerative colitis.
bowl disease were DR2, whereas 227 controls possessed this antigen ($\chi^2=9.92$; $p$ (corrected for 10 antigens)$=0.016$). Other B cell antigens and HLA-A,-B and -C specifities showed no significant difference from controls.

Individuals possessing DR2 were, therefore, nearly 40% less likely to develop inflammatory bowel disease than controls (relative risk 0.63:1). The relative risks for Crohn’s disease and ulcerative colitis for individuals possessing DR2 were 0.63:1 in each case. These results suggest that the possession of DR2, or a closely related and yet unidentified gene, may diminish the chances of an individual developing inflammatory bowel disease. The data are consistent with the idea that genetic influences are important in the aetiology of inflammatory bowel disease. However, additional work is required to clarify the gene or group of genes responsible.

**T84**

Impairment of chemotactic migration of polymorphonuclear leucocytes in inflammatory bowel disease may be due to ingestion of immune complexes

A P KIRK, D G GODDARD, E J HOLBOROW, AND J E LENNARD-JONES (Department of Gastroenterology, St Mark’s Hospital, London, and Bone and Joint Research Unit, London Hospital, Whitechapel, London) Chemotaxis through 3μ cellulose ester filters was used to study Sykes-Moore chambers. Peripheral polymorphonuclear leucocytes were obtained from patients with Crohn’s disease (20 patients), ulcerative colitis (24 patients), and normal controls (20). Impaired chemotactic migration was seen in both inflammatory bowel diseases compared with the controls ($p<0.05$) and this was independent of disease site and activity.

It was postulated that this defect in chemotaxis results from prior ingestion of immune complex. In order to investigate the effect of immune complex on normal leucocyte migration, polymorphonuclear leucocytes from 10 control subjects were preincubated with stabilised aggregates of human IgG (20–50S) with immune complex-like properties. Chemotactic migration immediately afterwards was significantly reduced ($p<0.05$). It was possible to visualise IgG within the cells by immunofluorescence.

In the patients circulating immune complexes were detected by the Cl₉ binding assay in 16% of those with ulcerative colitis and 27% in Crohn’s disease. Circulating polymorphonuclear leucocytes from an additional series of patients were stained with fluorescein labelled anti-human immunoglobulin and cytoplasmic IgG inclusions, but not IgA or IgM, were detected by immunofluorescence in 55% of patients with Crohn’s disease and 40% of those with ulcerative colitis, but in none of the controls. Impaired leucocyte chemotaxis in these patients might thus be due to ingestion of circulating immune complex.

**PANCREATOBILIARY PHYSIOLOGY**

**T85–T93**

**T85**

Action of exogenous cholecystokinin on pancreatic polypeptide

P G DEVITT, S GUZMAN, J LONOVICS, P L RAYFORD, AND J C THOMPSON (introduced by M H THOMPSON) (Departments of Surgery, The University of Texas Medical Branch, Galveston, Texas, USA, and the Bristol Royal Infirmary, Bristol) Previous studies have shown the importance of cholinergic mechanisms in the control of secretion of pancreatic polypeptide (PP). We have investigated the role of cholecystokinin (CCK) in the release of PP.

Six healthy volunteers were studied. 99% pure CCK was sterilised by filtration and biological activity confirmed using an isolated gallbladder bioassay. Two doses of CCK were infused (0-25 and 0-5 μg/kg-h) and the plasma PP and CCK responses compared with those after a meal in the same individuals.

Basal concentrations of PP were 165±47 pmol/ml and these rose to a peak of 424±76 pmol/ml with the low dose, and 504±129 pmol/ml with the high dose of CCK. The peak value seen with the meal was 922±318 pmol/ml. The integrated response of PP to CCK was less than the response to food (36 and 43%). Integrated values of CCK were 5.9±0.9, 18.2±2.3 and 6.0±2.6 ng-min/ml with the infusion of 0-25 and 0-5 μg/kg-h of CCK and after food respectively.

We conclude that CCK, in doses that could be considered physiological, releases PP; the quantity of PP released was a minor proportion of the total response of PP to food, suggesting that other mechanisms are more important in the release of PP.

**T86**

Physiological importance of extra-pancreatic sources of pancreatic polypeptide

P G DEVITT, A AYALON, R YAZIGI, P L RAYFORD, AND J C THOMPSON (introduced by M H THOMPSON) (Departments of Surgery, The University of Texas Medical Branch, Galveston, Texas, USA, and the Bristol Royal Infirmary, Bristol) Most pancreatic polypeptide (PP)-cells are found within the pancreas, and all, or nearly all, circulating peptide is thought to originate from the pancreas. Increased quantities of PP-like immunoreactivity have been found in the antrum compared with the rest of the bowel, and we have studied the possible physiological significance of this finding.

Total pancreatectomy was performed in six dogs. Basal PP concentrations fell from 62±14 pmol/l to 21±4 pmol/l one hour after pancreatectomy. A bolus dose of bombesin (500 ng/kg) increased plasma concentrations of PP in both the antral (peak value 40±8 pmol/l) and femoral (peak value 24±4 pmol/l) vein.

In another group of dogs, 10% liver extract (LE) was instilled from the antrum or duodenum. The portal, antral and the femoral vein were cannulated. Basal values of 81±22 pmol/l in the antral vein were increased to a peak of 113±31 pmol/l on antral perfusion with LE. Similarly intestinal perfusion with LE increased antral venous concentrations of PP. These increased PP concentrations were still raised 60 minutes after cessation of the LE infusion.

We conclude that (1) extrapancreatic sources of PP do contribute to basal circulating concentrations of the peptide and (2) PP in the antrum may be released into the circulation by physiological stimuli.

**T87**

Pancreatobiliary diversion (PBD) by duodenal transposition: a new model for stimulating jejunal and pancreatic adaptation

B MIAZZA, H LEVAN, S VAJA, AND R H DOWLING (Gastroenterology Unit, Department of Medicine, Guy’s Hospital and Medical School, London) Studies of PBD are important for two reasons:
first, if PB secretions (PBS) are trophic to the intestine, theoretically jejunal deprived of PBS should become hypo-
plastic. Secondly, the intestinal hypo-
plasia of total parenteral nutrition is prevented by intravenous secretion and CCK but it is not known if these hormones act directly on the gut or indirectly through the pancreas. Before studying this during TPN, in six to nine orally-fed male Wistar rats we diverted PBS from the jejunum by transposing the duodenum to mid small intestine and eight days later compared resultant changes in structure and function of pancreas and of six equal-
length segments of jejunum and ileum with those from sham-operated controls.

Results showed that in PBS-deprived jejunum (pool results segments 1–3) mucosal wet weight (mg cm−2 intestine) increased from 37.3±SEM 3-7 to 55.2±6.1 (p<0.0025) with corresponding changes in mucosal protein (p<0.005–0.001), DNA (p<0.005), and quantitative histo-
logy. In ileum, we confirmed a trophic effect of PBS with significant increases (p<0.05–0.001) in mucosal wet weight, protein, and DNA cm−2 for segment 4 with lesser changes in segments 5–6. After PBD, pancreatic wet weight, protein and DNA doubled (p<0.001), the amylase and trypsin content of whole pancreas did not change but specific activity fell—trypsin 20.2±2.8 to 9.6±3.8 μEq min−1 mg DNA−1 (p<0.01) and amylase from 488±148 to 189±55 U mg DNA−1 (NS).

To summarise: duodenal transposition not only stimulates hyperplasia in ileum, it also provokes marked hyperplasia of both jejunum and pancreas.

T88
Effect of topical bile salt on pancreatic duct mucosal permeability to bicarbonate
C J SIMPSON, H J E LEWI, AND D C CARTER (University Department of Surgery, Royal Infirmary, Glasgow) It has been sug-
gested that a pancreatic duct mucosal barrier restricts movement of HCO3− from duct lumen into blood stream, and that increased HCO3− loss induced by luminal bile salt may be implicated in the pathogenesis of acute pancreatitis.

The pancreatic duct of anaesthetised cats was cannulated at either end in 14 animals. Changes in volume and net Cl− and HCO3− flux were measured during perfusion at constant pressure, with bicarbonate solution containing 120

mmol/l HCO3− (BS) or bicarbonate solu-
tion containing added sodium tauro-
cholate in concentrations from 5 to 40 mM (BS + T). All solutions were made isotonic with cat plasma by adding mannitol.

Perfusion with (BS + T) increased net loss of luminal HCO3− and increased net gain of luminal Cl−. The magnitude of ion flux was related linearly to tauro-
cholate concentration for both HCO3− (r=0.93) and Cl− (r=0.96), but HCO3− loss and Cl− gain were not on a 1:1 basis. Extrapolation of regression lines to zero taurocholate concentration gave a y intercept of +1.5 for Cl− and −1.9 for HCO3−. This would indicate that an exchange of HCO3− and Cl− ions across the pancreatic duct mucosa occurs under basal conditions and that the addition of taurocholate increased the permeability to these monovalent ions.

These findings confirm that topical bile salt increased ion flux across the pan-
creatic duct and show that the increase is dose-dependent.

T89
Increase in perfusion pressure potentiates taurocholate-induced damage in the pancreatic duct
C J SIMPSON, H J E LEWI, AND D C CARTER (University Department of Surgery, Royal Infirmary, Glasgow) It has been sug-
gested that a pancreatic duct mucosal barrier restricts movement of HCO3− from duct lumen into blood stream, and that increased HCO3− loss induced by luminal bile salt may be implicated in acute pancreatitis.

The pancreatic duct of anaesthetised cats was cannulated at either end in 14 animals. Changes in volume and net Cl− and HCO3− flux were measured during perfusion at a constant rate with a bicarbo-
nate solution (BS) containing 120

mmol/l HCO3−, or bicarbonate-tauro-
cholate (BS + T) solution containing added sodium taurocholate in a concentration of 40 mM. With a constant rate of perfu-
sion, mean intraduct pressure was 3.7

(±SE 0.85) mmHg. An additional series of experiments was performed during which the BS + T was perfused at a constant rate but with intraduct pressure held at 30 mmHg.

Perfusion with 40 mM taurocholate under basal perfusion pressure increased both HCO3− loss and Cl− gain. These changes in ionic flux were significantly potentiated by increased perfusion pres-
sure. The results support the thesis that pancreatic duct damage by bile salts is compounded by a raised intraduct pressure.

T90
Isolated main pancreatic duct: a new model
J N FOX, J L AUSTIN, AND H A REBER (Intro-
duced by T V TAYLOR) (Harry S Truman Memori-
al VA Hospital and Department of Surgery, University of Missouri, Columbia, USA) After ligating side branches, seg-
ments (1-5 cm) of cat main pancreatic duct were excised, cannulated, and placed in a physiological solution. Standard perfusate (SP), ([Na+] 150, [Cl−] 30,

[HCO3−] 120 mEq/l 300 mOsm/l) was per-
fluenced through the duct at controlled rates, and changes in [HCO3−] and [Cl−] of SP measured. Permeability was also studied after exposure to acidified SP and/or NaCN. The response to secretin and cholecystokinin was determined by measuring the volume, [protein] and [anion] of collected perfusate and the transudal potential difference (PD).

Results showed that perfusate [HCO3−] decreased and [Cl−] increased reciprocally at perfusion rates <0.07 ml/h. Osmolarity was unchanged. Permeability remained normal for at least four hours, was increased after perfusion with SP, pH2.3, but recovered within one hour. When 5 mM NaCN was added to the perfusate recovery did not occur. Secretin or cholecystokinin in perfusate or surrounding solution did not change either the volume recovered, [HCO3−], [Cl−] or [protein]. Transudal PD was related to transudal [HCO3−] gradient (−1 to −2 mV); changing by −1.6 mV when secretin was present in either bath or perfusate and returned to normal when secretin was removed.

We conclude that the in vitro duct is similar to the in vivo duct and is a valid model for the study of factors affecting main duct permeability.

T91
Simple colorimetric method for assay of biliary phospholipids
M K DUTT, BARBARA MURRAY, AND R P H THOMPSON (Gastrointestinal Research Laboratory, Rayne Institute, St Thomas's Hospital, London) Measuring biliary phospholipids is essential for determining
the cholesterol saturation index of bile. Currently, this is carried out indirectly by digesting phospholipids with perchloric acid and measuring the inorganic phosphorus produced. Contamination with phosphorus from other sources necessitates using special acid-washed glassware. The procedure is lengthy and perchloric acid potentially explosive. We have adapted a simple, direct method, for measuring amniotic fluid lecithin, to bile, using ordinary glassware.

Human bile was extracted by a modified Folch procedure with chloroform:methanol (C:M). A dilution of the final extract was mixed with dodecamolybdophosphoric acid (DDMPA) to form a lecithin-molybdophosphate (L-M) complex via lecithin’s quarternary nitrogen. Uncomplexed DDMPA was removed with water. The L-M complex remaining in the lower organic phase was reduced to molybdenum blue with stannous chloride. The resulting stable colour formed immediately and its absorbance was measured at 720 nm. A standard curve of lecithin in methanol was linear to 0.5 mM.

Perchloric acid digestion of the biliary lipid extracts gave closely similar results. The regression line correlating the two is described by \( y = 1.07x - 0.61 \) (intercept mM/L), \( r = 0.98 \), \( p < 0.001 \), \( n = 12 \). The coefficient of variation ranged from 2.9-7.4%. Lyssolecithin and sphingomyelin, both with quarternary nitrogens, also reacted with DDMPA but phosphatidyl ethanolamine, with a primary nitrogen, did not.

This method is direct, simple, rapid and safe.

T92
Do meals alter plasma bile acid clearance?

J H Marigold and R P H Thompson (Gastrointestinal Research Laboratory, Rayne Institute, St Thomas’ Hospital, London) The plasma disappearance of \(^{14}\)C-glycocholic acid (\(^{14}\)C-GCA) after intravenous injection is reported to be the same before and after a meal. As this finding is theoretically unlikely, the fasting plasma disappearance curves of 5 \(\mu\)Ci \(^{14}\)C-GCA and 0.25 mg.Kg-1 indocyanine green (ICG) were compared with those obtained 100 minutes after a standard liquid test meal in nine healthy subjects. Another four subjects received ICG alone. The plasma disappearance rate was faster postprandially, as reflected in the significant but variable increase in plasma clearance of \(^{14}\)C-GCA (median 455 ml.min\(^{-1}\).m\(^{-2}\), range 376-672 increased to 704, 528-1968; \( p < 0.01 \)) and ICG (359, 227-473 increased to 435, 358-985; \( p < 0.01 \)). Median initial volume of distribution was unaltered for either \(^{14}\)C-GCA (3679 ml.m\(^{-2}\), 2148±5401 and 3667, 2362-931; \( p > 0.05 \)) or ICG (1404, 810-2632 and 1510, 1001-2058; \( p > 0.05 \)), but in four subjects it was greatly increased postprandially. No alteration in plasma volume, measured with Evans Blue, was observed postprandially in five subjects.

The increased clearances of \(^{14}\)C-GCA and ICG are probably related to the increased liver blood flow that occurs postprandially. It suggests that clearance of bile acids by the liver, like other parts of their enterohepatic circulation, also varies with meals, so that, as predicted, clearance is increased after a meal, or conversely falls during fasting.

T93
Bilirubin solubility by mixed micelles and interaction with cholesterol and calcium

M K Dutt, Barbara Murray, and R P H Thompson (Gastrointestinal Research Laboratory, Rayne Institute, St Thomas’ Hospital, London) Patients with cholesterol gallstones have bile supersaturated with cholesterol but so may normal subjects, while such stones often have pigment and calcium at their centres. Unconjugated bilirubin (UCB) is present in bile but insoluble in water. We have investigated its solubilisation by micelles and the effect on this of cholesterol and calcium.

We have avoided the difficulties of using solid bilirubin by (a) co-precipitating sodium taurocholate (NaTC), lecithin (L), cholesterol and UCB from chloroform: N,N-dimethylformamide (C:DMF, 1:1) to give supersaturated micelles, (b) adding colloidal bilirubin to unsaturated micelles. Judged by infra-red spectroscopy C:DMF left compound unchanged and without DMF contamination. After equilibration, solubilised bilirubin was measured in 220 nm Millipore filtrates. Methods (a), approaching equilibrium from supersaturation, and (b), from unsaturation, gave the same results.

Maximum UCB solubility was 1.2 mM which is much greater than reported. Physiological concentrations of cholesterol reduce this, giving a sigmoid curve for bilirubin solubility. Increasing the NaTC:L ratio to reduce cholesterol solubility shifts the curve to the left. Calcium also sharply reduced bilirubin solubilisation.

We propose that UCB, driven from the micelle by cholesterol, complexes with calcium and precipitates more pigment. Bilirubin and calcium are probably important in stone nucleation; cholesterol, however, retains key roles by occupying the micelle and also constituting the bulk of a stone.
and an improvement has not been demonstrable after two years.

F2
Duodenoscopic sphincterotomy in the elderly

A S MEE, A G VALLON, J R CROKER, AND P B COTTON (Gastrointestinal Unit, The Middlesex Hospital, London) Duodenoscopic sphincterotomy is an increasingly popular alternative to conventional surgical management of bile duct stones, which is particularly hazardous in the elderly. Between January 1975 and December 1979 we attempted duodenoscopic sphincterotomy in 70 patients aged more than 70 years (mean age 76 years, eldest 103 years); 12 patients still had their gall-bladders. Sphincterotomy was possible in 68 (97%) and duct clearance was achieved in 65 (96%). The two failures of sphincterotomy were due to substantial peri-papillary diverticula; the three retained stones were large (20, 38, and 40 mm diameter). The largest stone extracted was 24 mm in diameter.

There were no deaths, but significant complications occurred in nine patients (13%); haemorrhage in four (requiring surgery in one), cholangitis in four (two of whom required surgical stone extraction), and pancreatitis in one. The average length of hospital stay in successful cases was 11 days (range three to 30 days). There has been no evidence of stone recurrence or sphincter stenosis during clinical follow-up in 51 of the patients from six months to five years.

Duodenoscopic sphincterotomy is a major advance in the management of elderly patients with common duct stones.

F3
Isotonic Vivonex causes water secretion in normal human jejunum

B J M JONES, B E BROWN, AND D B A SILK (Department of Gastroenterology, Central Middlesex Hospital, London) Diarrhoea limits the use of enteral nutrition in a significant number of patients. The aim of this study was to determine whether there is a basic constituent ofenteric diets which has a secretory effect on the normal human jejunal mucosa. Five normal subjects were intubated with a double lumen perfusion tube with a proximal occlusive balloon. Twenty-five cm segments of proximal jejunum were perfused with isotonic solutions of the elemental diet, Vivonex HN (2.6 g nitrogen/l; 17 mmol Na+/l.), and the whole protein based diet Ensure (3.7 g nitrogen/l; 23.6 mmol Na+/l.). Exclusion of luminal amylose was confirmed. Water absorption (ml/25 cm/h ±SEM) was stimulated by Ensure (+130.0±24.3) but Vivonex caused marked secretion (−60.05±8.4; P<0.001). Vivonex also caused greater sodium secretion (−37.4 mmol/25 cm/h±3.0) than Ensure (−22.0±1.2; P<0.001) despite similar concentrations of infused sodium. Thus, in the absence of luminal hydrosolysis, the whole protein diet stimulated jejunal water absorption and reduced the net secretion of sodium because of the low luminal sodium concentration. Vivonex, like Ensure, contains glucose oligosaccharides known to stimulate jejunal sodium and water absorption. Despite this, Vivonex had a secretory action in the normal human jejunum which may be one of the reasons why patients on this diet develop diarrhoea.

F4
Neuron specific enolase as a new cytochemical marker for neuroendocrine cells of the gut and pancreas and related tumours

F J TAPIA, J M POLAK, A J A BARBOSA, P FACER, P J MARANGOS, AND A G E PEARSE (Department of Histochernistry, RPMS, Hammersmith Hospital, London, and Clinical Psychology Branch and the Laboratory of Clinical Science, NIMH, Bethesda, USA) Neuron specific enolase (NSE) is an acidic protein first isolated from bovine brain by Moore. Additional studies demonstrated this enolase to be an isoenzyme specific to neurones. We here report on the use of antibodies to NSE as a new cytochemical marker for both neural and endocrine components of the diffuse neuroendocrine system in health and disease. Using a number of different fixatives in both liquid and vapour form and the peroxidase-antiperoxidase technique, we studied the presence of NSE-like immunoreactivity in normal gut and pancreas of man and rat and in human neuroendocrine tumours. All regulatory peptide containing cells including enterochromaffin cells, as well as autonomic nerves and intrinsic neuronal cell bodies, reacted strongly to the antibodies. Neuroendocrine tumours (N=67) also showed NSE-like immunoreactivity: 18 out of 23 vipomas, 11 out of 13 gastrinomas, eight out of nine insulinomas, 11 out of 12 glucagonomas, and six out of 10 intestinal carcinoids. Tumour cells reacted strongly to NSE antibodies regardless of the amount of stored peptide. We conclude that (1) NSE is yet another product common to the neural and endocrine systems, which further emphasises their essential unity, and (2) NSE is a useful cytochemical marker for neuroendocrine tumours.

F5
Truncal vagotomy impairs the normal human enteric motor response to a meal

D L WINGATE, D G THOMPSON, AND H D RITCHIE (London Hospital Medical College, London) Using a pressure-sensitive radiotelemetric capsule stationed at the duodenal-jejunal flexure, jejunal motility was measured for a period between 18 and 24 hours, which included one standard 540 kcal meal, in non-operated chronic duodenal ulcer patients (n=9), asymptomatic truncally-vagotomised patients (n=7), and truncally-vagotomised patients with chronic diarrhoea (n=4).

Non-operated patients were identical to normal controls with respect to the incidence of fasting motor complexes (MCs) and the interruption of MCs by the meal (358±103 min). In the asymptomatic vagotomised patients, there was a significant (p<0.05) decrease in the interruption of MCs by the meal to 249±120 min. In the group with diarrhoea, the interruption of MCs by the meal (136±12 min) was significantly reduced in comparison with both the non-operated group (p<0.001) and the asymptomatic operated group (p<0.01).

These results demonstrate that duodenal ulcer disease does not impair normal jejunal motility, but truncal vagotomy impairs the motor response to a meal. The association of diarrhoea with the premature postprandial return of MCs suggests that the propulsion of digesta and bile acids into the colon by powerful peristaltic waves may contribute to the causation of diarrhoea.

F6
Duodenal ulcer recurrence after healing with cimetidine or tripotassium dicitrato bismuthate (DeNol)

D F MARTIN, D HOLLANDERS, S J MAY, M M RAVENSCroFT, D E F TWEEDLE, AND J P MILLER (Departments of Medicine and Surgery, University Hospital of South
Manchester, Manchester) Fifty seven patients whose duodenal ulcers had healed with either cimetidine (Tagamet) or tripotassium dicitrato bismuthate — TDB (DeNo1) were reviewed monthly as outpatients. Endoscopy was repeated when symptoms recurred or after six months and 12 months in some asymptomatic patients. The members of staff who performed follow-up assessment and endoscopy were unaware of the initial treatment each patient had received as were the patients themselves. The two treatment groups were similar with regard to age, sex, length of history, smoking habits, and use of alcohol. Of 27 patients given cimetidine 49% had relapsed after three months, 70% after six months, 85% after 12 months, and 90% after 18 months. Of 30 patients given TDB 14% had relapsed after three months and after six months and 46% had relapsed after 12 months and 18 months. This difference is highly significant, P < 0.001 by the log rank test. No patient was found to have asymptomatic recurrence after six or 12 months. Age, sex, and length of history did not appear to affect relapse.

These results show that relapse of duodenal ulcer is significantly less common after initial healing with TDB than with cimetidine.

F7
Rate and pattern of epithelial cell proliferation in ulcerative colitis

A P KIRK, E P SERAFINI, AND T J CHAMBERS (introduced by J E Lennard-Jones) (Department of Gastroenterology, St Mark's Hospital, London, and Department of Experimental Pathology, St Bartholomew's Hospital Medical College, London) The rate and pattern of proliferation of rectal mucosal cells in ulcerative colitis in remission and relapse were studied. While these have been reported as increased in active disease, there are no data on ulcerative colitis in remission.

Twenty-six patients with ulcerative colitis (15 total, 11 distal, mean duration 10.3 years) and seven controls were studied. Eighteen patients were in remission, judged clinically and histologically, and eight had active disease. Rectal biopsies were incubated with tritiated thymidine in vitro, and the rate and pattern of epithelial cell proliferation determined by autoradiography.

The rate of proliferation, expressed as percentage of labelled nuclei within the crypt, was similar in active colitis (19%) and remission (17.3%) and significantly greater than the controls (13.1%, P < 0.01). The pattern of proliferation was expressed as the ratio of cells proliferating in the lower two-thirds to those in the upper third of the crypt. This ratio was similar in active colitis (1.5) and remission (1.35) and significantly different from the controls (4.2, P < 0.01). There was no relation between the proliferative pattern and the extent and duration of the disease, or the drug therapy.

In conclusion there is an increased rate of epithelial cell turnover in both active and inactive ulcerative colitis. This may be related to the increased incidence of carcinoma arising in ulcerative colitis.

F8
Faecal occult blood screening in general practice

R MILLION, J HOWARTH, E TURNBERG, AND L A TURNER (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) All patients over 40 years of age in two general practices were approached by letter to participate in a screening programme for faecal occult blood. Of 3481 patients, 1131 (32.5%) failed to reply despite a second letter; 963 (27.7%) refused, and 1179 (33.9%) agreed to take part. A nurse visited the latter subjects and explained the test. A Haemoccult slide test was performed on two samples of each stool passed on three consecutive occasions. Of 1179 subjects tested, positive results were obtained in 32 (2.7%). These patients were investigated further and the following conditions discovered: two, carcinoma colon; three, colonic polyp; one, solitary rectal ulcer; one, proctitis; four, haemorrhoids; one each bleeding duodenal ulcer and hiatus hernia; two, 'heavy' aspirin ingestors; three, diverticular disease, and in 15 subjects no abnormality was detected despite full investigation including colonoscopy. Both excised carcinomata were Dukes's class A; no polyp was malignant. Although one practice was predominantly made up of council tenants and the other of owner occupiers, the acceptance rate was not statistically different in the two practices. The cost of this screening of 1179 subjects with discovery of two early cancers and three patients with bleeding polyps was approximately £6,400.

F9
Oral metronidazole in Clostridium difficile positive antibiotic associated diarrhoea

R P BOLTON (introduced by R E Barry) (University Department of Medicine, Bristol Royal Infirmary, Bristol) Oral metronidazole has been reported as being effective in the treatment of Clostridium difficile colitis after antibiotics. Clearance of toxin and organism, together with symptomatic improvement, occur with metronidazole, but many of the less severe cases are self-limiting and no controlled studies are available.

Twelve patients with Clostridium difficile positive antibiotic associated diarrhoea are described, six of whom received treatment with oral metronidazole (200 mg or 400 mg tds for seven to 10 days), while six received no specific therapy. Patients were paired according to duration of symptoms before diagnosis (mean eight days, range three to 11 days) and toxin titres, assayed in Hep 2 monolayer cell culture, were similar.

Symptomatic improvement with clearance of toxin was noted in all cases and the duration of symptoms from diagnosis to resolution was recorded. In the metronidazole treated group, the mean duration of symptoms was 5±3 days (range three to 10 days), while in patients receiving non-specific therapy, mean duration was 15±8 days (range 10–21 days) (P < 0.01).

It is concluded that oral metronidazole is effective in significantly reducing the duration of symptoms in patients with Clostridium difficile positive antibiotic associated diarrhoea.

F10
Prevention of experimental immune-complex colitis by hydroxychloroquine

J M ROHDES, J E MCLAUGHLIN, D J BROWN, L NUTTALL, AND D P JEWELL (Department of Medicine, Royal Free Hospital, London) Leucocyte-mediated injury is likely to be involved in the pathogenesis of ulcerative colitis. Hydroxychloroquine suppresses leucocyte chemotaxis so we have studied its effect on the development of immune-complex colitis in rabbits.

Twelve 2 kg male NZW rabbits were studied. Six were given 20 mg/kg hydroxychloroquine subcutaneously daily and six were given 0.4 ml saline subcutaneously daily. After three days all 12 rabbits received 1 ml 1% formaldehyde
rectally followed two hours later by 1ml intravenously of human albumin HSA/rabbit anti-HSA complexes in antigen excess. Rectal biopsies taken at 0, 24, and 120 hours were coded and graded from one to four for overall severity. Separate gradings were given for acute inflammation, goblet cell depletion, and chronic inflammation.

At 24 hours biopsies from treated rabbits showed overall less inflammation than the control animals, but this difference was not significant. However, the summated gradings for acute inflammation and goblet cell depletion had worsened significantly more in the control rabbits than the treated rabbits (changes in mean grade +6.7 and +1.8 respectively, p<0.05). There was no difference in the mononuclear cell infiltration between the two groups. By 120 hours the colitis was resolving in all rabbits.

This study demonstrates the usefulness of the immune-complex colitis model for initial drug assessment. Hydroxychloroquine effectively reduces the acute inflammatory infiltrate and merits trial in human ulcerative colitis.

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**CLINICAL MEDICAL**

**F11**

**When does gastro-oesophageal reflux occur in patients with peptic oesophagitis?**

**J N Blackwell and R C Heading (Department of Therapeutics and Clinical Pharmacology, Royal Infirmary, Edinburgh)**

Fifteen hour continuous monitoring of distal oesophageal pH has been performed in 22 patients with peptic oesophagitis. The studies ran from 5.30 pm to 8.30 am and patients were encouraged to eat a normal evening meal. The tracings were analysed with respect to the number of reflux episodes and the time that the distal oesophageal pH was below 5, within each hour. Gastrooesophageal reflux did not occur at a uniform rate during the studies. The highest number of reflux episodes occurred within the hour 7–8 pm, during which there was an average of six reflux episodes, resulting in a pH below 5 for an average of 23 minutes. This peak of reflux followed the evening meal and reflux remained considerable for three hours, such that this period included 55% of all reflux episodes and 52% of the total time that the pH was below 5. The frequency and duration of reflux then fell progressively, attaining the lowest levels at midnight, remaining low until 6 am when increased reflux was synchronous with the patients' awakening.

In these patients half of the total gastro-oesophageal reflux during the 15 hour studies occurred post-prandially during the early evening. By comparison, nocturnal reflux was comparatively infrequent, implying that oesophagitis is generated principally during the waking hours rather than during sleep as has been popularly believed.

**F12**

**Aspirin, paracetamol, and haematemesis and melena**

**D Coggon and M J S Langman (University Department of Therapeutics, City Hospital, Nottingham)**

Previous epidemiological studies of 'aspirin induced' upper gastrointestinal bleeding are flawed because they have relied upon hospital and not community controls and because equivalent questions were not asked about paracetamol intake so that an opportunity to include a drug control was lost. We compared the aspirin, paracetamol, and other drug intake of 346 patients with bleeding with that of community controls. Recent aspirin and paracetamol intake were both strongly associated with bleeding. For all time periods the association was stronger for aspirin than for paracetamol and for long-term use the association disappeared for paracetamol but not for aspirin.

The excess intake of paracetamol by haematemesis patients was principally for indigestion, and the numbers of patients and controls taking paracetamol for headache or colds did not differ. Aspirin consumption was more frequent among the haematemesis group for all indications.

A dose response relationship was evident between aspirin and bleeding but none was found for paracetamol. These results suggest that aspirin does cause gastrointestinal haemorrhage, but that the risk has been overestimated in the past because patients with haematemesis and melena take analgesics to relieve indigestion and symptoms associated with bleeding.

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**F13**

**Cimetidine or surgery for severe duodenal ulcer dyspepsia?: results of a three to four year follow-up**

**D L McWhinnie, G R Gray, J S Smith, and G Gillespie (Division of Surgery, Victoria Infirmary, Glasgow)**

Controversy exists regarding whether cimetidine or surgery offers the best solution for patients with severe duodenal ulcer dyspepsia. It has been shown that few such patients treated with maintenance cimetidine (400 mg nocte) required surgery over a six to 12 month period and furthermore it has been suggested that maintenance cimetidine may alter and improve the natural history of duodenal ulceration.

However, the further progress of such patients requires investigation. We report here the results of follow-up from a group of 60 patients who were originally selected as candidates for ulcer surgery but who instead entered a trial of maintenance cimetidine 400 mg nocte three to four years ago.

Forty-seven of the original 60 were available for follow-up and have been assessed clinically and endoscopically.

Seventeen required surgery within 14 months (35%). The remaining 30 have so far avoided operation, but no patient who discontinued cimetidine remained symptom-free while off treatment. The results of surgery for the 17 who failed on cimetidine appear no different from those in other previous surgical series.

**F14**

**Long-term treatment of duodenal ulceration with ranitidine**

**E J S Boyd, N R Peden, J H B Saunders, and K G Wormsley (Department of Therapeutics, Ninewells Hospital, Dundee)**

Eighty patients with endoscopically healed duodenal ulcers were entered into an open maintenance study with ranitidine 150 mg nocte. Thirty-six patients have been followed-up for more than six months and nine for more than one year. Endoscopy was performed at six and 12 months, or if symptoms recurred. The cumulative annual recurrence rate was about 30%. Some pathophysiological correlates of breakthrough will be discussed. Symptomatic gastro-oesophageal reflux was common (15%) even in the absence of ulcer recurrence or macroscopic oesophagitis. Treatment was well tolerated and there were no side-effects requiring drug withdrawal.
Basal levels of FSH, LH, prolactin, oestradiol, and testosterone were measured before treatment and at two weeks, four weeks, and 26 weeks in male patients receiving ranitidine 300–320 mg/ day for one month followed by maintenance. These were compared with a matched group receiving cimetidine 1000 mg/day for one month followed by maintenance (1000 mg/day). Hormone levels were unchanged in patients receiving ranitidine. In those receiving cimetidine basal levels of testosterone increased and remained raised. LH levels rose significantly in the cimetidine group at two weeks but then returned to pre-treatment levels. These results indicate a direct anti-androgenic effect of cimetidine not found with ranitidine and therefore probably not related to H₂-receptor blockade.

F15
Does gluten cause the enteropathy and the skin lesion in dermatitis herpetiformis (DH)?

J N BLACKWELL, R ST C BARNETSON, H M GILMOUR, A FERGUSON, AND R C HEADING (University Departments of Therapeutics, Dermatology and Pathology, Royal Infirmary of Edinburgh, and Department of Medicine, Western General Hospital, Edinburgh) Five patients with DH, who had gone into remission with disappearance of skin rash while taking a gluten-free diet, were subjected to gluten challenge. Skin and multiple jejunal mucosal biopsies were obtained before and after challenge with 20 g gluten daily.

The challenge produced jejunal mucosal changes similar to those seen in coeliac disease. Mitotic counts within crypts and disaccharidase assays were the most sensitive indices of mucosal damage. However, the skin rash recurred in only two patients, the other three patients remaining free of rash after 1½, 1½, and two years of continued gluten ingestion. Subepidermal IgA deposits were present in all patients before the gluten challenge, and there was no apparent change in the density of IgA deposits after gluten challenge.

Dietary gluten clearly induces the jejunal abnormality of DH, but the relationship of gluten and gluten enteropathy to the skin rash is much less clear-cut. We have confirmed that some patients should continue taking a gluten-free diet as primary treatment for the skin lesion as well as the enteropathy. However, malabsorption in DH is rare and in those patients whose rash does not recur after gluten reintroduction, the benefit of prolonged gluten exclusion is questionable.

F16
Gluten-induced mucosal changes

M DOHERTY AND R E BARRY (Department of Medicine, University of Bristol, Bristol Royal Infirmary, Bristol) Coeliac disease seems to result from a combination of genetic and environmental factors. Previous work suggests that gluten sensitivity may be dose dependent. Thus excess gluten intake may be one environmental factor which precipitates the onset of disease. We have studied the effect of a large gluten intake on (1) five normal controls, (2) four normal blood relatives of coeliac patients, and (3) four patients suffering from immunological disturbances (primary biliary cirrhosis, common variable immune deficiency, IgA deficiency).

HLA status was recorded. Jejunal architecture, serum gluten and autoantibodies and xylose absorption were studied on a normal diet and again after six weeks on a diet containing an additional 40 g gluten per day for six weeks.

No architectural changes occurred in the jejunal mucosa of normal controls. The changes of partial villous atrophy occurred in groups 2 + 3 as indicated by fall in the ratio villous height/mucosal thickness from 0.799 ± 0.34 on normal diet to 0.714 ± 0.075 on gluten enriched diet. Changes in absorption or antibody status were not detected. Subtotal villous atrophy did not occur.

We conclude that excessive gluten intake can induce changes in the jejunal mucosal architecture in susceptible individuals who do not have overt coeliac disease.

F17
Which laboratory data best measure Crohn's disease activity?

C ANDRE, P LANDAIS, AND J FERMANIAN (introduced by R N Allan) (Unité 45 INSERM, Service d'Hépato-Gastro-Entérologie, Hôpital E. Herriot, Lyon and Unité 88 INSERM, Centre de Calcul, Hôpital de la Pitié Salpêtrière, Paris) The Crohn's Disease Activity Index developed by the National Co-operative Study Group in the USA has proved too cumbersome for routine use, and the recently proposed simplified clinical index remains open to the criticism that it is necessarily subjective. This has led to the suggestion that at least one laboratory parameter should be included. We have compared 11 different laboratory measurements in assessing the activity of Crohn's disease in 54 patients. The laboratory results were compared with the CDAI by stepwise multiple regression analysis. The disease activity was severe in 14 patients, moderate in 12, minor in 14, and quiescent in 14. Activity was best defined in decreasing order by orosomucoid, sedimentation rate, C reactive protein, alpha-1-antitrypsin, albumin, haematocrit, IgM, circulating immune complexes, serum iron, IgG, and IgA. The haematocrit, the only laboratory measurement in the CDAI, is less discriminant than acute phase reactants. Only three parameters—namely, orosomucoid, sedimentation rate, and C reactive protein—have a significant weight and should be complementary to the simple clinical index.
from 1971 census data. There were two peaks of incidence for proctocolitis—in the 4th decade and 8th decade; the latter gave the highest incidence (15/10000/year). This pattern of incidence was true for proctitis and more extensive colitis and was more marked for women than men.

F19
Natural history of proctocolitis in the North-east of Scotland: a community study
T S Sinclair, P W Brunt and N A G Mowat (Gastroenterology Research Unit, Royal Infirmary, Aberdeen) Grampian Region with its stable population, centralised records, and excellent case retrieval is recognised as an ideal area for epidemiological studies of disease in a community.

In an extensive retrospective survey covering the decade 1967–76, a total of 537 new patients with non-specific proctocolitis (NSP) were identified. A 97% follow-up was achieved.

A striking finding was an average annual incidence of 11·3 per 100,000, about twice the highest recorded elsewhere. An apparent rise in incidence was noted over the study period. A bimodal age distribution was confirmed. However, in contrast with the Oxford study, female preponderance was not found. (M/F ratio 1·15/1·00). The urban incidence exceeded the rural. The frequency of both NSP and Crohn's disease in first degree relatives was strikingly high.

The youngest and oldest age groups had the most extensive colonic involvement and the severest clinical attacks at onset. 

Actuarial analysis was performed to assess the natural history of NSP. Risk of relapse over five years did not correlate with the extent of disease at onset. Surprisingly the risk of relapse diminished with increasing severity of the first attack. Furthermore, the risk of relapse decreased with increasing age of onset.

F20
Effect of loperamide, codeine phosphate and diphenoxylate on urgency and incontinence in chronic diarrhoea
C L Corbett, K R Palmer, and C D Holdsworth (Gastroenterology Unit Royal Hallamshire Hospital, Sheffield) Urgency and incontinence are major disabilities of patients with chronic diarrhoea, but their control by drugs has not been studied.

Thirty patients had randomised double-blind treatment with each drug for one month. Before treatment all had troublesome diarrhoea and 95% admitted to urgency and occasional incontinence. Individual adjustment of dosage was made during the first 10 days on each drug until there was adequate control or side-effects supervened.

Each drug was equi-effective in reducing stool frequency to a mean of 1·8 to 1·9 stools daily, the mean daily amount taken being 4·6 mg loperamide, 103·5 mg codeine phosphate, and 12·5 mg diphenoxylate. Failure to complete treatment because of poor control or side-effects occurred on diphenoxylate in five patients, on codeine phosphate in four patients, and, largely because of constipation or abdominal pain, on loperamide in four patients.

Diphenoxylate was much less effective in producing a solid stool than the other two drugs (p<0·01) and was also least effective in relieving urgency and incontinence. As it also had significantly more side-effects (p<0·05) we conclude that it is a less satisfactory drug than loperamide or codeine phosphate.

CLINICAL SURGICAL
F21–F30

F21
Should the choice of operation for duodenal ulcer depend on preoperative gastric secretion?
P B Boulos, P F Whitfield, and M Hobsley (Department of Surgical Studies, The Middlesex Hospital and Medical School, London) Several workers have suggested that patients especially liable to recurrence of peptic ulceration after gastric surgery can be distinguished on the basis of preoperative acid secretion. This hypothesis has been tested in 68 patients with duodenal ulcer who were studied before vagotomy by (1) histamine infusion test (0·13 nmol kg⁻¹ hr⁻¹) and (2) insulin test (0·2 U/kg intravenously). Follow-up after vagotomy was for at least two years and recurrence was diagnosed by endoscopy and/or at laparotomy.

Preoperative secretion data were corrected for pyloric losses and duodenal stomach reflux (Vₜ) and height standardised. The indices examined were plateau maximal Vₜ, 1–2Vₜ (secretion volumes half to two hours after insulin), and the ratio of these two indices that quantifies parietal cell mass and vagal drive.

None of these preoperative secretory indices bore any relation to the incidence of ulcer recurrence after vagotomy. It is concluded that the magnitude of the parietal cell mass or of the vagal drive does not affect the chance that a vagotomy will fail to prevent recurrent ulceration. There appears to be no foundation for a policy of 'tailoring' the form of acid reducing operation to the results of preoperative secretion studies.

F22
Selection of patients suitable for revisional gastric surgery
S Sagar, J S Grime, and R Shields (Departments of Surgery and Nuclear Medicine, Royal Liverpool Hospital, Liverpool) The selection of patients who may benefit from revisional gastric surgery is critical, especially if endoscopy and barium studies have been unhelpful. Additional operations are not only difficult but may also increase morbidity without alleviating symptoms. Survey of literature showed that symptoms were relieved by revisional surgery in only 65% of patients (2,257 out of 3,476). The mortality rate was 4·1% (144 patients). These unsatisfactory results (35% failure) are possibly due to patients selection, as radiology and endoscopy were of diagnostic help in only 60%. An investigation which could identify those patients who are likely to benefit from revisional surgery would be very valuable. This would not only improve results of surgery but also prevent further complicated operations in those patients in whom operations would be of no benefit.

A study was undertaken to determine whether such patients' symptoms could be explained by investigating gastric emptying as certain functional disorders displayed characteristic emptying patterns.

We investigated 30 patients with normal endoscopy and radiology, who were being considered for further operation because of their symptoms. In 12 patients abnormalities such as gastric re-filling or rapid or delayed emptying were seen. Nine of these patients have undergone revisional operations and are now asymptomatic. The remaining three await
surgery. Re-operation has been avoided in 10 patients in whom gastric emptying pattern was normal. In eight patients, marginal abnormalities of emptying have been successfully treated with appropriate medication. The different types of emptying profiles will be displayed, and their interpretation discussed.

F23
Is it true that women fare worse after gastric surgery than men?

E J WHELDON, C W VENABLES, J D CRANAGE, and I D A JOHNSTON (Department of Surgery, University of Newcastle upon Tyne, Newcastle upon Tyne) Most surgeons are under the impression that the results of gastric surgery are worse in women than men. This has caused a reluctance to operate upon women unless complications occur. Since 1968 we have undertaken a prospective study of all patients undergoing gastric surgery on our unit using a standardised documentation system and organised by a doctor not involved in the surgical care. In the present study we have examined the results in men and women found at one, two, and five year follow-up intervals after truncal vagotomy and pyloroplasty (V and P) and Billroth I (GI) gastrectomy. So far 378 (62 women) patients after V and P and 49 (23 women) after BI have been followed up for at least five years. A detailed comparison of symptoms has been undertaken and this reveals that, with a few exceptions, there are no differences in the symptoms found in women compared with men.

It is concluded that there is no justification for the belief that women will fare worse than men after gastric surgery, as far as symptoms are concerned.

F24
Which is the best route for antibiotic prophylaxis in gastric resection?

M HARES, D GATEHOUSE, T MUSCROFT, D W BURDON, M R B KEIGHLEY (The General Hospital, Birmingham) Post-surgical sepsis is common after gastro-oesophageal resection, but there are few antimicrobial studies which have been confined to gastro-oesophageal surgery. The risk of sepsis is related to bacterial colonisation of the stomach, and is rare if the gastric pH is 4.0 or less.

We report a trial started in June 1977 among 81 consecutive patients having gastro-oesophageal resection or bile diversion. Patients were randomly allocated to a single preoperative dose of systemic cefuroxime (n=27), intra-incisional cefuroxime (n=26), or placebo (n=28). The groups were similar for age and diagnosis, but oesophago-gastrectomy was more common in the systemic group. The results of the study are summarised. Anastomotic dehiscence was recorded in seven placebo patients compared with nine receiving systemic prophylaxis. In 21 patients with postoperative sepsis, 16 had preoperative bacterial counts greater than 105. However, the gastric microflora were a poor indicator of the organisms which caused clinical sepsis.

The study indicates that cefuroxime is a suitable antibiotic for gastro-oesophageal operations and that only systemic administration significantly reduced the incidence of sepsis. Although high risk patients may be detected by pH or bacterial count, the potential pathogen cannot be easily predicted by preoperative gastric bacteriology.

F25
Timing of biliary surgery in gallstone-associated acute pancreatitis (AP)

D H OSBORNE, C W IMRIE, and D C CARTER (University Department of Surgery, Royal Infirmary, Glasgow) The effect of the timing of biliary surgery on outcome in gallstone-associated pancreatitis was reviewed in 144 patients (part of a prospective study of AP). Eighteen per cent of patients were known to have gallstones before their original episode of AP. Biliary surgery was performed during the first admission in 30 patients (group 1), while 58 went home to be readmitted for elective operation (group 2). Another 33 patients required emergency readmission with recurrent AP/biliary colic (group 3), and the remaining 23 were unwilling or unfit for surgery. Objective prognostic grading of severe AP identified patients who fared badly but included many who had an uncomplicated clinical course. Overall mortality was 9.4%. There was no significant difference in mortality or incidence of severe AP among the three groups.

Mean delay from initial attack of AP to time of definitive surgery differed in the three groups: group 1 =16 (± 8) days; group 2 =118 (± 119) days; group 3 = 461 (± 1112) days, and the increased morbidity associated with recurrent attacks of AP/biliary colic suggests that early surgery in selected cases is the procedure of choice. In patients with severe AP, an individually orientated policy regarding the timing of biliary surgery is necessary.

F26
Reappraisal of sepsis after biliary tract surgery

D H LEVIE, T BATES, M HARRISON, and J W A REUTHER (William Harvey Hospital, Ashford, Kent) The high incidence of sepsis after biliary surgery and its prediction by gram-stain and culture of the bile have been re-examined in a prospective study of 95 cholecystectomies. The wound infection rate was 4.2% and one patient developed septicaemia. Nineteen patients (20%) had infected bile but, although only three of these received prophylactic antibiotics, none developed clinical sepsis. A gram-stain of bile at operation failed to show organisms in seven of the 19 patients with a positive culture and there was one false positive.

Three of the 13 jaundiced patients developed a wound infection (23%) compared with one of the remaining 82 patients (1-2%, p < 0.01). Two of the 13 patients over 70 years developed a wound infection (15%) compared with two of the 82 patients under 70 (2-4%) NS.

In the present study, wound sepsis after biliary surgery was less than previously reported and the presence of infected bile failed to predict subsequent sepsis.

F27
Percutaneous extraction of gallstones via the T-tube track

R R MASON, A G VALLON, and P B COTTON (Department of Radiology and Gastrointestinal Unit, The Middlesex Hospital, London) Since July 1977, 64 patients have been referred with retained common bile duct stones demonstrated by T-tube cholangiography; 22 patients were treated by duodenoscopic sphincterotomy, and 42 were managed by percutaneous stone extraction after a five week postoperative delay to allow development of the T-tube track.

In 10 patients with T-tubes size 16 FG or greater, an experimental fibreoptic cholecodochoscope was used to visualise the bile duct, and the stones removed by
F28 Predicting the need for surgery in small-intestinal Crohn's disease

JANE M BRADSHAW AND R F HARVEY (Gastroenterology Unit, University Hospital, Bristol) In a prospective study over a three-year period, 92 patients with Crohn's disease affecting the small intestine were investigated. At entry all patients were examined, a simple Crohn's disease activity index obtained, and blood was taken for various tests, including measurements of erythrocyte sedimentation rate (ESR), or-acid glycoprotein, plasma viscosity, and fibrinogen. Clinical and laboratory indices of Crohn's disease activity correlated rather poorly. Thus in 12 patients the simple Crohn's disease activity score was 5 or more, corresponding with troublesome symptoms, yet the ESR and other 'inflammatory' tests were normal. During the three year period of follow-up, 11 of these 12 (91.7%) have required operation for intractable symptoms arising from their small-intestinal Crohn's disease, compared with only three of 80 (3.8%) in the rest of the group (p<0.01). Obstruction (eight patients), fistula (two patients) and bleeding from ileal ulcers (one patient) were the indications for operation in these 11 patients.

We conclude that measurement of the simple Crohn's disease activity index in conjunction with some simple blood test for inflammation, such as the ESR, seems to predict accurately the need for surgery in most patients with symptomatic small-intestinal Crohn's disease.

F29 Management of acute sigmoid volvulus

J R ANDERSON AND D LEE (Gastro-Intestinal Unit, Western General Hospital and Department of Clinical Surgery, Royal Infirmary, Edinburgh) Considerable controversy exists regarding the best method of treatment of patients with acute sigmoid volvulus. A retrospective analysis of 134 patients over a 13 year period has been undertaken.

When the colon was viable, non-operative deflation per rectum followed by interval sigmoid colectomy carried the lowest mortality (3/31). This is similar to previous reports. In patients not fit for surgery, deflation alone carried a high incidence of recurrence (9/18) but these patients have been successfully redeflated without mortality.

Emergency laparotomy will be required in one third of cases because (1) of failure to make the diagnosis preoperatively, (2) of failure of initial deflation, or (3) non-viable bowel is suspected. Only the patients treated by Hartmann's procedure survived when gangrene was present (3/13). When the colon is viable a variety of surgical procedures are possible. The mortality rates after the Mikulicz resection (5/26), sigmoid colectomy and primary anastomosis with proximal defunction (3/20) or without defunction (3/16) and operative detorsion with or without colopexy (2/8) are similar and no one procedure can be advocated for all situations. To prevent long-term recurrence resection must be carried out. Whenever doubt exists as to the advisability of any of the procedures mentioned, Hartmann's operation has much to commend it.

F30 EEA autosuture in sphincter conservation

W O KIRWAN (Department of Surgery, Regional Hospital and University College, Cork) Autosuture techniques are being widely introduced for low colorectal anastomosis in the management of rectal cancer. The reliability of the technique is sub judice.

Experience with the first 30 cases using the EEA instrument is reported. All patients had a Hypaque enema at 10 days postoperation to test the integrity of the anastomosis. In four cases the anastomosis was between colon and squamous anal epithelium.

In the first 10 cases there were four radiological subclinical anastomotic leaks. In the second 10 cases there were two leaks and in the latest 10 cases there were no radiological leaks. Defunctioning the colostomy has been abandoned in the last five cases without mishap.

The ratio of anterior resection to abdominoperineal resection is now 10:1 in our unit and abdominoperineal resection is becoming a rare procedure. There is no doubt that EEA anastomosis is vastly more reliable low in the pelvis than conventional sutured anastomosis and that temporary defunctioning colostomy can frequently be avoided.

PATHOLOGY

F31 Toxin production by enterobacteria in tropical malabsorption (TM) and giardiasis but not in blind loop syndrome (BLS)

B S DRASAR, SARAH GYSELYNN, AND A M TOLKINS (Department of Medical Microbiology and Clinical Nutrition and Metabolism Unit, Hospital for Tropical Diseases, London School of Hygiene and Tropical Medicine, London) The production of toxin by enterobacteria (EBC) from the upper intestine of patients with TM and giardiasis has been compared with that in BLS by measuring the cytopathic effect of bacteria-free filtrates on Vero cells. Previous studies have shown that these cells are sensitive to a wider range of toxins than Chinese hamster ovary and Y-1 adrenal cells. Of the EBS isolated from 21 patients with TM (Klebsiella pneumoniae in 13, E coli in four, Serratia marcescens in two, and Citrobacter in two), there were seven which produced cytopathic effects. Of the EBC isolated from eight patients with giardiasis (Klebsiella pneumoniae in five, E coli in one, Serratia marcescens in one, and Enterobacter cloacae in one) there were five which produced cytopathic effects.

However, none of the EBC from nine patients with BLS (E coli in seven, Klebsiella pneumoniae in one, and Serratia marcescens in one) produced any cyto-
Institute of Pathology, cytology the firms considerable Photography F32
Photography and coagulation biopsy confirms the diagnosis of angiodysplasia

J D BUCHANAN AND R H HUNT (Departments of Pathology and Gastroenterology, Royal Naval Hospital, Haslar) Vascular ectasias are increasingly recognised as a cause of colonic bleeding.

The pathogenesis and pathology have been comprehensively reviewed and complicated techniques are required to identify these lesions in surgical specimens. We have found that colonoscopy with in vivo photography followed by coagulation biopsy provides accurate diagnosis with pathological confirmation, and often successful treatment without surgery.

Vascular ectasias in 14 patients presenting with episodic rectal bleeding and melena were confirmed by photography supported by coagulation endoscopic biopsy (10) and the gross lesions removed at right hemicolecotomy (two).

Biopsies were processed and stained by routine methods; coagulation artefacts secondary to the biopsy technique did not present any problems in biopsy interpretation.

Normal biopsies were often obtained when the lesion was confined to the submucosa but photography supported the pathological diagnosis. Early mucosal ectasias showed dilated thin-walled submucosal veins communicating with small groups of abnormal dilated venules and capillaries between normal crypts. Advanced lesions showed extensive destruction of normal architecture with replacement by dilated vessels in which only vessel wall lay between vascular lumen and colonic contents.

Photography and coagulation biopsy can provide pathological confirmation of the majority of small vascular ectasias diagnosed and treated by colonoscopy.

F33 Comparative evaluation of biopsy and cytology sampling in the upper and lower gastrointestinal tract

F HALTER, A DOLDER, U SCHEURER, AND P GREILLAT (Gastrointestinal Unit and Institute of Pathology, University Hospital, Inselspital, Berne, Switzerland) Apparent differences in the diagnostic yield of multiple endoscopic biopsies (mb) and brush cytology (bc) prompted us to evaluate their comparative merits in a total of 4907 gastroscopies and 1806 colonoscopies performed in our unit since 1976.

Eight hundred and fifty-nine ulcerative or proliferative lesions were submitted to both mb and bc sampling at the same examination. Histological and cytological examinations were performed by two independent teams. In 226 verified oesophago-gastric malignancies the diagnostic yield of mb and bc was similar (75 and 70% respectively). Cumulative accuracy amounted to 88% and was significantly (p < 0.05) higher than that of either procedure alone. The respective data for 77 colonic malignancies were 60% for mb and 87% for bc (p < 0.0005). The cumulative accuracy was 95% and not significantly higher than that of bc alone. In both series the false positive rate was well below 1%. Mb thus yielded significantly (p < 0.05) better results in the stomach, while bc was more accurate in the colon (p < 0.05). Although seldom used in clinical practice, colonic cytology can therefore be regarded as a very valuable diagnostic method.

F35 Bacterial L forms and inflammatory bowel disease: a relationship

W C WATSON, M R BELSHEIM, R DARWISH, AND S N SULLIVAN (GI Unit, Victoria Hospital and University of Western Ontario, London, Canada) The purpose of this study was to determine whether bacterial L forms could be recovered from biopsies obtained from Crohn's disease (CD) and ulcerative colitis (UC) patients, and from controls without inflammatory bowel disease. Tissue from 82 IB patients (36 CD, 46 UC) and 51 controls was placed immediately into a sterile hypertonic transport medium and stored at 40°C for one to three days. Biopsies were then manually homogenised, plated onto fresh media, and incubated at 37°C. Standard media were employed for isolation of parental organisms and the same media made hypertonic, specially enriched and containing 1000-10 000 U/ml penicillin G were used for L form culture. Homogenised tissue was plated directly onto parental media but was passed through a 220 nm filter before being plated onto L form media.

L forms of E. coli, Strept fecalis, Pseudomonas aeruginosa, Aerococcus viridans, Proteus mirabilis, and Entero- bacter cloacae were recovered from 13 CD patients, 23 UC, and no controls. This indicates that the bowel environment in IBD favours L form growth and induction while normal bowel does not. If L forms are responsible for the clinicopathological features of IBD it seems likely that more than one type is involved.

F36 Cl. difficile toxin in inflammatory bowel disease

M R KEGHLEY, M JOHNSON, R H GEORGE, R N ALLAN, AND D W BURDON (The General Hospital, Birmingham) Two recent reports have suggested that the toxin
A G Johnson (University Departments of Surgery and Pathology, Royal Hallamshire Hospital, Sheffield) The hypothesis that duodenal ulcers are caused by a failure in epithelial cell proliferation was investigated in 10 control patients with normal duodenum, 10 with perforated ulcers, and 10 undergoing elective ulcer surgery.

Control biopsies were taken from the bulb and distal first part of duodenum at endoscopy or operation involving duodenotomy. In ulcer patients biopsies were taken from ulcer edge and distal normal-looking mucosa. Biopsies were incubated with ^3H-thymidine for 30 minutes and autoradiographed for four weeks. The labelling index was calculated from the mean percentage of crypt nuclei incorporating ^3H-thymidine in samples of 1500 nuclei, results being compared by the Wilcoxon rank sum test.

The labelling index of ulcer edge biopsies was significantly higher than that of controls (perforations 19 ± 2.0%; elective ulcers 17 ± 1.7%; controls 8.4 ± 0.4%, mean ± SEM. p < 0.01). In ulcer patients with ulcer edge biopsies there was a significant increase in labelled cells. Normal mucosa distal to ulcers had a labelling index similar to that of controls. Pathological grading of biopsies showed the labelling index significantly increased in both ulcer grades 2, 3, and ulcer edge.

Epithelial cell proliferation was therefore active in ulcer patients with no evidence for a generalised or localised failure in the DNA-synthesis phase of epithelial renewal.

The British Society of Gastroenterology

F37 Histological study of the effects of oesophageal sclerotherapy

D M D Evans, D B Jones, B K Cleary, and P M Smith (Departments of Gastroenterology and Pathology, Llandough Hospital, South Glamorgan) Twenty-eight patients with cirrhosis and bleeding varices have been treated by oesophageal sclerotherapy. In 10, the varices have disappeared and the patients have not bled again. Eight have come to necropsy, three dying from malignant tumours of the liver, three from bleeding varices, one from hepatic failure, and one from cardiac failure, at intervals ranging from one to 51 days after the last injection of sclerosant. They received from one to seven treatments.

At necropsy, multiple sections of the oesophagus have been studied by the technique of Mochizuki (1972). Analysis shows extensive thrombosis of veins in the mucosa, submucosa, muscularis propria, and adventitial connective tissue. Necrosis and ulceration is liable to follow submucosal injection with healing by fibrosis leading to stricture formation in some. The findings provide guidance in the use of sclerotherapy for the control of oesophageal varices.

F38 Epithelial cell proliferation in duodenal ulcer

C J Bransom, M E Boxer, J C Clark, and A B Price (Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex) Acute diarrhoea is a common cause of admission to an infectious disease unit. This study aimed to survey the causative bacteria using extensive microbiological methods, to compare the frequency of the various aetiologies, and to delineate the clinical groups. In 12 months 73 adults were admitted who had a clinical diagnosis of acute infectious diarrhoea. Campylobacter spp. and salmonella spp. were the commonest isolates, 26 (34%). There were only five virus isolates and three cases of giardiasis. In 13 patients (17%) diarrhoea followed antibiotic therapy, yet C. difficile toxin was detected in only two. It was also the cause in two patients not receiving antibiotics. This organism is clearly not the main cause of diarrhea associated with antibiotic therapy yet conversely will produce acute diarrhea when antibiotics are absent. In 22 patients no bacterial pathogens were isolated and there was no history of antibiotics. Fifteen of these had rectal biopsies and seven showed definite inflammatory changes in the crypts. They suffered a short diarrhoea illness with leukocytosis, a minimal fever, pain and bloody stools which was contrasted with the protracted illness caused by the recognised pathogens. This relatively distinct group are a
microbiological challenge. They may harbour a new pathogen, form a link with chronic non-specific inflammatory bowel disease, or both.

GASTRODUODENAL PHYSIOLOGY
F41–F50

F41
Studies of the gastric 'mucus-bicarbonate barrier: the influence of aspirin and acetyl cysteine on the pH gradient across gastric mucus in vivo

I N ROSS, H M M BAHARI, AND L A TURNBERG (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) Secretion of mucus and bicarbonate together may protect gastric mucosa from intraluminal acid and this is supported by the demonstration of a stable pH gradient across rabbit gastric mucus in vitro. We have examined the influence of potential damaging agents on the pH gradient across gastric mucus in the anaesthetised rat in vivo. With the luminal surface bathed in HCl (mean pH 2.01) the stable pH on the epithelial side of the mucus layer was 6.01±0.72 (n=8) measured with an antimony pH microelectrode. Aspirin 10−2M in pH 2.01 HCl in the luminal solution caused an appreciable fall in pH gradient within one to four minutes reaching 30%±11 (n=8) by 15 minutes, the gradient being almost entirely abolished by 30 minutes. The gradient remained absent or reduced only in the area exposed to aspirin and was normal in unexposed areas of the same stomach. The mucolytic agent n acetyl cysteine (5% solution) in the luminal medium, almost entirely abolished the pH gradient within 10 minutes.

These results confirm the presence of a pH gradient in vivo in rat gastric mucus. This gradient can be compromised by agents known to interfere with either the mucus itself or with bicarbonate secretion.

F42
Histamine and peptic ulcer: assay and identification of histamine in human gastric juice by a fluorometric-fluoroenzymatic technique

J V PARKIN, W LORENZ, H BARTH, D WEBER, AND M L CROMBACH (Department of Experimental Surgery and Pathological Biochemistry, University Surgical Clinic, Marburg/Lahn, West Germany) H2-receptor antagonists reduce gastric acid response to histamine and pentagastrin but not carbachol. The exact role of histamine in parietal cell control is disputed. Gastric mucosal histamine is low in duodenal ulcer, probably representing increased release, but histamine in gastric aspirate previously proved impossible to measure.

A sensitive and specific assay for histamine in gastric aspirate has been developed and will be described. This allows measurement of concentrations as low as 0.1 ng/ml. Specificity is shown by kinetic studies using histamine methyltransferase from pig corpus mucosa, by using formaldehyde to prevent fluorophore formation and by destroying the fluorophore by heating. Quality control results will be given, as will data for recovery of known quantities of added histamine. Sources of error and contamination are identified.

The results of a pilot study on histamine in gastric juice in subjects with duodenal ulcer, gastric ulcer, and without peptic ulceration will be given (mean 16.4, median 10.4, range 6.7–38.2 ng/ml), and the implications for our understanding of the control of gastric acid secretion discussed.

F43
Gastric emptying of lipids in man: a new scintigraphic method of study

R JIAN, J Y NAJAN, AND J J BERNIER (Research Unit on Pathophysiology of Digestion, Hôpital Saint-Lazare and Department of Nuclear Medicine, Hôpital Saint-Louis, Paris, France) Gastric emptying of lipid is still a matter of debate and no information exists about the reciprocal rates at which lipids and solids leave the stomach. The new availability of a γ-emitting lipid marker, 32P-glycerol triether (32P-GTE), allowed us to approach these problems by a tubeless scintigraphic technique.

Seven volunteers ate a solid-liquid meal labelled with the 32P-GTE (incorporated into the butter) and with 99mTc-sulphur colloid (99mTcS), as a hydrodissolvable phase marker. Emptying rates of the two markers were measured by detection of radioactivity changes over the gastric area by a γ-camera, at regular intervals. Emptying of a solid phase marker (99mTcS bound to cooked egg whites) was measured using the same meal on a separate day.

Empting rate (expressed as percentage ingested activity emptied/min; mean±SD) of lipids (0.24±0.13) was markedly lower (p<0.001) than that of the rest of the meal (0.57±0.11) and slightly lower (p<0.05) than that of solids (0.38±0.07). An intra gastric layering of fat above water was observed only after the first postcibal hour and remained moderate.

We conclude that, after ingestion of an ordinary meal, lipids leave stomach markedly slower than aqueous phase and slightly slower than solids. This discrimination is not only due to a layering of lipids above water.

F44
Physiological basis of solid-liquid discrimination in human gastric emptying

R C HEADING, J REID, T V TAYLOR, AND P TOTHILL (University Departments of Therapeutics and Clinical Pharmacology, Clinical Surgery and Medical Physics, Royal Infirmary of Edinburgh, Edinburgh) In dogs, the effect of partial gastrectomy on gastric emptying of solid food is greatly influenced by the nature of the surgical reconstruction. To investigate its importance in man, we have measured gastric emptying using dual isotope labelling of liquid and solid elements of a mixed meal in 17 control subjects, in seven patients with Billroth I and nine with Polya gastrectomy and in patients with truncal vagotomy and pyloroplasty (TV+P) (14 patients) or gastroenterostomy (TV+GE) (11 patients). All were six months or more postoperative.

In the partial gastrectomy patients, liquid and solid emptied together throughout the two hour study period. In contrast, both groups of vagotomised patients exhibited a more normal pattern, with solid emptying more slowly than liquid (TV+P p<0.01; TV+GE p<0.05). However, solid-liquid discrimination was not seen during the early (0–10 minute) period. Emptying patterns in patients with and without postoperative diarrhoea were generally similar. In all patient groups, early emptying tended to be greater than in controls.

The results imply that, in man, antral function alone determines solid-liquid discrimination in emptying. This function is not destroyed by TV+P or TV+GE but no discrimination occurs during early emptying. The duodenum is not an important influence on the postoperative emptying pattern.
F45
Effects of ranitidine and cimetidine on gastric and salivary secretion induced by bethanechol in the anaesthetised dog

JANET M HUMPHRAY, M J DALY, AND R STABLES (introduced by J J Misiewicz) (Department of Pharmacology, Glaxo Group Research Limited, Ware, Hertfordshire) Ranitidine and cimetidine inhibit not only histamine and pentagastrin but bethanechol-induced gastric secretion in the Heidenhain pouch dog. To establish whether these H2-antagonists have any antimuscarinic activity we have measured both salivary volume and gastric acid secretion in the dog.

Beagle dogs (6-9 kg) were anaesthetised and prepared for measurement of blood pressure and heart rate. Gastric secretion was collected from an acute fistula and salivary secretion from a cannula in the left parotid duct. Gastric and salivary secretions were stimulated by a continuous intravenous infusion of bethanechol (3 μg kg⁻¹ min⁻¹).

Intravenous bolus doses (mg kg⁻¹) of ranitidine (0-03-1 0), cimetidine (0-10-3 0, or atropine (0-001) were administered, each dose to at least three dogs.

Ranitidine and cimetidine each caused dose-dependent inhibition of gastric secretion. Anti-secretory ED50 values mg kg⁻¹ (95% confidence limits) were 0.082 (0.049-0.123) for ranitidine and 0.486 (0.280-0.845) for cimetidine. Neither ranitidine nor cimetidine had any significant effects on salivary volume. However, atropine (0-001 mg/kg) reduced gastric secretion by 85.9±2.7% and salivary volume by 47.0±8.9%.

Thus, in the anaesthetised dog, ranitidine was six times more active than cimetidine as an inhibitor of bethanechol-induced gastric secretion. Neither ranitidine nor cimetidine reduced salivary volume, indicating that, unlike atropine, neither drug has antimuscarinic activity.

F46
Serum pepsinogen in normal subjects and in peptic ulcer and its modifications after ranitidine treatment

F DI MARIO, M PLEBANI, F VIANELLO, R FARINI, A GIORDANO, G SCALABRIN, G CERIOTTI, AND R NACCARATO (Cattedra Malattie Apparato Digerente, Università Padova, Laboratorio Centrale Analisi, Ospedale Civile, Padova, Italy) In order to verify the physiological and pathological variations of total s-pepsinogen (a not extensively studied gastric secretory parameter), its fasting levels were evaluated in 68 normal subjects, in 48 patients with gastric ulcer and in 102 with duodenal ulcer, by means of the Ute method. The response to 15 g protein meal and to pentagastrin (6 μg/kg intramuscularly) in 18 volunteer normal subjects and the modifications after four weeks of 300 mg daily ranitidine treatment in 10 duodenal ulcer patients were also investigated.

Results showed that (1) total s-pepsinogen level was found to be higher in males (45.4±19 μg t/r/ml/24h) than in females (31.8±12.9; 2p<0.005); (2) it was significantly increased after meals (2p<0.02) and after pentagastrin (2p<0.01); (3) it was found to be significantly augmented in both gastric (62.2±29; 2p<0.001) and duodenal ulcer (76.3±41.8; 2p<0.001); (4) in gastric ulcer its serum level was significantly higher when the lesion was located at the antrum (75±30.1; 2p<0.05) or at the angulus (68±22; 2p<0.05) than at the corpus (51±20.6); (5) significant increase of s-pepsinogen was detected in duodenal ulcer after ranitidine treatment (49.5±21.5 before; 98.8±42.1 after; 2p<0.01); values similar to basal levels were documented after stopping the drug for at least 24 hours.

We conclude that total s-pepsinogen—simply and cheaply determined—is an accurate index of gastric secretion. As a consequence, we believe that s-pepsinogen may be used as a sensitive and reversible consequence of ranitidine action.

F47
Relationship between histamine and insulin stimulated secretion

P B BOULOS, R G FABER, P F WHITFIELD, AND M HOBSEY (Department of Surgical Studies, The Middlesex Hospital and Medical School, London) Histamine infusion of 0.13 nmol kg⁻¹ hour⁻¹ and insulin 0.2 μg/kg intravenously tests were performed in 81 duodenal ulcer patients and in 81 patients after vagotomy for duodenal ulcer. Before vagotomy insulin-secretion (I) averaged 70% of histamine-secretion (H). There was a significant correlation between (I) and (H) (b=1.003, rβ=0.74, p<0.001). After vagotomy (I) averaged 50% of (H) irrespective of the adequacy of vagotomy. There was no correlation between (I) and (H) after adequate vagotomy but after inadequate vagotomy there remained a significant correlation (b=072, rβ=0.001).

Forty-three patients had (H) and (I) studies before and after operation. (H) after adequate vagotomy was the same as H-I difference before vagotomy (T=148, NS). This is compatible with the view that vagal innervation sensitises the parietal cells to histamine. After inadequate vagotomy H-I was still the same as H-I difference before operation (T=41, NS). This finding, however, is not compatible with vagal sensitisation, as H-I after inadequate vagotomy should be a fraction of H-I difference before vagotomy.

This study suggests that there are two types of parietal cells, one responds to histamine only if vagally innervated and the other responds to histamine whether innervated or not. This may explain why in humans, unlike animals, it has not been possible to restore the maximal output after vagotomy to the preoperative output with high doses of stimulants or with cholinergics. Postoperative histamine tests should therefore provide a measure of the adequacy of vagotomy.

F48
Hormonal regulation of interdigestive activity in man?

(Departments of Medicine, University of Erlangen, Germany, and Hammersmith Hospital, London) The aim of the present study was to investigate (1) basal plasma levels of motilin, somatostatin, and pancreatic polypeptide and (2) the influence of exogenously administered somatostatin on the motor function of the upper gastrointestinal tract and the duodenal alkali-load during interdigestive state.

Cyclic somatostatin infused at a rate of 1-25 μg/kg/h induced motor complex (MMC)-like activity within duodenum and jejunum after 8.8±1.4 min (n=9), thus significantly (p<0.01) shortening the normal duration of an interdigestive cycle (11.5±18.9±6.3 min). Somatostatin-induced motor activity was blocked by atropine (0.012 mg/kg intravenously). The duodenal alkali load during somatostatin-induced complex-like activity (n=10) amounted to 1.87±0.22 mmol. There were no significant differences to the spontaneous activity data. Somatostatin plasma levels remained unchanged during the interdigestive state. Motilin and
pancreatic polypeptide showed a cyclical pattern significantly correlated with motor and secretory activity.

We conclude that (1) in spite of its known inhibitory effects on gastrointestinal motor and secretory function, somatostatin induces interdigestive complex-like intestinal motor and secretory activity; (2) this effect seems to be mediated by cholinergic pathways; (3) peripheral plasma levels of somatostatin remain unchanged during interdigestive state; (4) plasma PP and motilin show similar pattern with maximum levels related to the interdigestive complex; (5) therefore they may be modifying interdigestive activity.

F49
Insulin and glucose concentrations before and after feeding in duodenal ulcer patients

D J Sanders, S Zahedi-Asl, N F Knight, and C W Venables (Departments of Physiology and Surgery, Medical School, Newcastle upon Tyne) Hypoglycaemia stimulates gastric acid secretion partly by vagal stimulation.

Seven endoscopically proven duodenal ulcer (DU) patients and seven nondyspeptic age and sex-matched controls were given a standard breakfast and blood was taken at intervals before and after the meal. Plasma was assayed for gastrin, glucose, insulin, total and pancreatic glucagon.

The mean peak plasma insulin concentration in controls occurred 15 minutes after the end of the meal and was 47±14 mU/litre. In DU patients the insulin concentration continued to increase for 45 minutes to a value of 105±15 mU/litre, which was significantly higher than in control subjects from 30 to 75 minutes after the breakfast. Plasma glucose concentrations in DU patients were significantly lower than controls before and from 75 minutes after the end of the meal. The plasma pancreatic glucagon concentration was unaffected by the meal and was not significantly different in the two groups. Total glucagon was not significantly increased in the control group but it was significantly increased during the period 15 to 120 minutes after the meal in the DU patients.

It appears that the increased insulin concentration in the plasma of duodenal ulcer patients may be due to a greater insulin releasing effect by the plasma on the islets of Langerhans ('incretin effect'). The resultant hypoglycaemia may be sufficient to stimulate the vago and cause the hypersecretion of acid and pepsin often associated with DU disease.

F50
Release of VIP (vasoactive intestinal peptide) in dumping provocation

G R Sagar, M G Bryant, M A Ghatei, R M Kirk, and S R Bloom (Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, and Department of Surgery, Royal Free Hospital, London) Peptides, such as neurotensin, raised in the dumping syndrome are not vasoactive at levels found in this condition. Infusion studies of VIP in man and pigs have reproduced important features of dumping. The release of VIP was therefore investigated during dumping provocation.

Thirteen gastrectomy and seven control subjects were given 200 ml 50% oral glucose and blood glucose, VIP and haematocrit estimated. Gastrectomy patients had greater VIP levels (mean peak = 24±1 pmol/l) than controls (mean peak = 7±3 pmol/l, p < 0.001) and a more rapid increase of VIP (0.58 pmol min-1.1) than controls (0.05 pmol min-1.1, p < 0.001). Comparison of fasting and glucose-stimulated plasmas by gel chromatography revealed that the increase of VIP immunoreactivity was identical with purified porcine VIP. The rise of VIP in gastrectomy patients correlated significantly with the rise of blood glucose (r = 0.76, n = 13, p < 0.01) and the rise in haematocrit per minute (r = 0.79, n = 13, p < 0.001).

When gastrectomy patients were divided into those with and without postprandial dumping, the dumpers had higher VIP levels (mean peak = 33±5 pmol/l, n = 6) than asymptomatic patients (mean peak = 18±2 pmol/l, n = 7, p < 0.02) and a faster VIP rise (0.7±0.1 pmol min-1) than nondumpers (0.4±0.1 pmol min-1, p < 0.05).

Our study suggests that VIP, probably by virtue of its vasodilatory action, may be one of the factors in the pathogenesis of dumping, although its clinical importance requires further elucidation.