The British Society of Gastroenterology

The 42nd Annual Meeting of the British Society of Gastroenterology was held at the University of Exeter, Exeter, on 22–25 September 1981 under the Presidencies of Professor A E Read 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 Professor Henri Sarles on 'Chronic pancreatitis and alcohol consumption'. Abstracts of the papers read at the meeting are printed below.

T1
Effect of the weight and the composition of a meal on its transit through the small intestine in man

N W READ, CHRISTINE BROWN, AND CHRISTINE EDWARDS (Department of Physiology, The University of Sheffield, Sheffield) The effect of varying the weight and composition of a meal on its gastric emptying and small intestinal transit was investigated in controlled experiments in 21 healthy volunteers. Each subject drank 100 ml water with the meal. Doubling the weight of each absorbable dietary component but keeping the unabsorbable component constant prolonged gastric emptying (2.1±0.1 vs 1.6±0.1 h, P<0.005), did not alter the transit time of the head of the meal, but prolonged the transit time of the bulk of the meal (7.5±0.5 vs 6.9±0.4 h, P<0.005). Increasing the amount of unabsorbable carbohydrate while maintaining constant the weight and total calories did not significantly influence gastric emptying but reduced the transit time for both the head (2.4±0.2 vs 4.4±0.2) and the bulk of the meal. The presence of fat in the meal slowed gastric emptying (1.3±0.2 vs 1.1±0.1 h, P<0.05) but did not significantly alter small bowel transit times. Finally, feeding a second meal 2½ hours after a first meal reduced the transit time of the first meal (3.1±0.1 vs 4.0±0.3 h, P<0.01), causing it to enter the caecum half an hour after ingesting the second meal.

T2
One in five emergencies with angina are due to oesophageal disease

H ALBAN DAVIES, D B JONES, AND J RHODES (Department of Gastroenterology, University Hospital of Wales, Cardiff) Oesophageal anginal pain is often overlooked in emergency admissions where no evidence is found for ischaemic heart disease. We have examined several simple tests to identify oesophageal disease in this situation.

Seventy-five consecutive admissions with angina were investigated and 23 of them had no evidence of ischaemic heart disease, even after an exercise tolerance test. The oesophagus was studied in these and proved responsible for symptoms in 11 patients and the probable culprit in another five. Only three patients remained a diagnostic but not a clinical problem.

No single test was infallible in identifying relevant oesophageal abnormalities in the 16 patients. Oesophageal acid perfusion tests were positive in seven of 14, oesophagoscopy and biopsy were abnormal in eight of 13 and radiology in eight of 15. Oesophageal spasm was shown by manometry in six of 15 patients but was evident only after ergometrine provocation in one of them.

In order to diagnose accurately whether the oesophagus is responsible for symptoms, it appears necessary to investigate patients presenting with angina but without evidence of ischaemic heart disease with a series of tests. The single most helpful test in reproducing the patient's pain was oesophageal acid perfusion.

T3
Familial rumination: a new (or neglected) syndrome

D LEVINE, D L WINGATE, E R WOZNIK, AND J T HARRIES (London Hospital, Whitechapel, London E1 and Hospital for Sick Children, London) We report five patients with a familial rumination syndrome. This is characterised by repeated, effortless regurgitation of food starting from 15 minutes to two hours after a meal. The food is still palatable and is usually chewed and swallowed again. There is no associated dysphagia, nausea, or heartburn.

Three patients, aged 7, 30, and 47 years, represented successive generations of one family. Two other adults both reported that one parent had habitually ruminated. In these families, parental rumination was not considered particularly abnormal and was usually described within the family as 'chewing the cud' or 'eating a meal twice'. The one child in this series and two others seen without a family history had been referred because of halitosis.
Conventional barium meals and oesophageal manometry were normal in these patients. When rumination was once observed radiologically after a barium/food mixture, sudden gastric compressions were noted. This appeared to result from diaphragmatic descent but other mechanisms involving cricopharyngeal relaxation must also occur.

Unlike previously reported cases, none of our patients displayed important psychopathology on testing. We suggest that this is a habit disorder which may depend on a parental model. Clinical recognition can prevent much unnecessary investigation.

T4 Comparative study of different doses of acarbose, pectin, a combination of acarbose and pectin, and placebo in the dumping syndrome

P A J SPETH, J B M J JANSEN, AND C B H W LAMERS (Division of Gastroenterology, St Radboud-Hospital Nijmegen, The Netherlands) Recently it has been shown that acarbose, an α-glucosidase inhibitor (Bayer), reduces the symptoms of postoperative dumping after an oral gift of 50 g sucrose.

In a double-blind study we compared the effect of 50 mg and 100 mg acarbose, 4-2 g pectin, 50 mg acarbose with 4-2 g pectin, and a placebo on plasma glucose, plasma insulin, breath hydrogen, and a dumping score after a normal carbohydrate-rich breakfast. Nine patients were studied (eight male, one female, aged 28–52 years). Seven had partial gastrectomy, two truncal vagotomy and pyloroplasty. All patients had symptoms of dumping and a hypoglycaemia of less than 3-0 mmol/l between 90 and 150 minutes after ingestion of 50 g glucose/m² body surface.

We found that 50 mg acarbose induced a significant flattening of the glucose curve and a significant improvement of the dumping score (P<0.05). Pectin significantly improved the dumping score, but did not significantly influence the other parameters. One hundred milligrams of acarbose or the combination of 50 mg acarbose and 4-2 g pectin were not more effective than 50 mg acarbose. Both doses of acarbose and the combination of acarbose and pectin led to significant increases in breath hydrogen.

This study shows that acarbose is effective in the treatment of dumping after a normal meal. Of the treatments studied, 50 mg acarbose was the preferable therapy.

T5 Increased pancreatic polypeptide in chronic alcohol abuse

R S FINK, T E ADRIAN, D MARGOT, AND S R BLOOM (Department of Chemical Pathology, Royal Free Hospital, London, and Department of Medicine, Royal Postgraduate Medical School, London) Alcohoism is a major scourge of modern society but its influence on gastrointestinal hormones is unknown. Ten young, chronic alcoholic men were studied, with 10 age-matched healthy controls. All subjects were in a good state of nutrition and were without other obvious disease. The postprandial gastrointestinal hormone profile was measured one and 14 days after sudden and complete alcohol withdrawal.

Basal plasma pancreatic polypeptide (PP) concentrations were significantly greater in alcoholics (control 28±5 pmol/l, alcoholics one day 62±14 P<0.05, 14 days 89±17 P<0.005). The total integrated PP responses (TIR) after a standard breakfast were similarly raised (control 442±63 pmol/l/180 min, alcoholics one day 1310±231, P<0.005, 14 day 1066±160, P<0.005). Basal and TIR values for gastrin, gastric inhibitory peptide, insulin and glucagon were similar in alcoholics and controls.

It is striking that, in spite of the high concentrations of alcohol which may continuously bathe the intestinal lumen, its effect on gastric and small-intestinal endocrine cells is minimal. In contrast, although alcohol concentrations reaching the pancreas are much lower, this organ is frequently involved in alcoholic disease. The secretion of PP, which is localised within both the exocrine and endocrine elements of the pancreas, is greatly influenced by alcohol abuse. As PP inhibits pancreatic enzyme secretion, this finding may have considerable significance.

T6 Cimetidine improves steatorrhoea and nutrition in cystic fibrosis

D M CHALMERS, R C BROWN, J KELLEHER, J M LITTLEWOOD, P C N CLARKE, AND M S LOSOWSKY (Departments of Medicine and Paediatrics, St James’s University Hospital, Leeds, and Department of Paediatrics, Harrogate District Hospital, Harrogate) The initial studies showing that addition of cimetidine to pancreatic supplements improved malabsorption in cystic fibrosis were too brief to demonstrate any improvement in nutrition. We have studied the effect of eight weeks’ cimetidine in 14 outpatients with cystic fibrosis aged 5–19 years.

Cimetidine 25 mg/kg/day was given 30 minutes before meals, and pancreatic enzymes towards the end of meals. Two-dish stool collections were made before treatment (week 0), after two, four, and eight weeks of treatment, and four weeks after stopping cimetidine (week 12). Patients were maintained on a constant fat diet, and results were corrected using a non-absorbable marker (PEG 4000).

Two patients were excluded because of incomplete collections. Mean faecal fat fell from 46.5 g/day in week 0 to 29.4 (P<0.05), 30.4 and 33.8 g/day in weeks two, four, and eight respectively. This represented a 25% improvement in fat absorption. Mean faecal nitrogen fell from 3.91 g/day to 2.74, 3.12, and 3.02 g/day. The improvement in steatorrhoea and azotorrhoea was not maintained after stopping cimetidine.

Median values for increases in height and weight after eight weeks’ therapy were 1–0 cm and 0–65 kg respectively. Haemoglobin rose 0-7 g/dl and median plasma vitamin A increased by 14 μg/dl (P<0.01). Median vitamin E level increased by 52 μg/dl. No adverse effects of cimetidine treatment were noted.

Thus, cimetidine improves fat and nitrogen absorption in cystic fibrosis and appears to produce nutritional benefit. The treatment is practicable and well-tolerated. Longer-term studies, with controls, of the clinical and nutritional value are required.

T7 5-aminosalicylic acid versus hydrocortisone in topical treatment of ulcerative colitis

M CAMPieri, G A LANFRANCHI, G FRANZI, G BAZZOCCHI, C BRIGNOLA, F SARTI, P R DAL MONTE, A BATTOCCHI, AND G LABO (introduced by D P Jewell and S C True-love) (I. Clinica Medica, Policlinico S. Orsola, Bologna, Italy) Sulphasalazine is established as an effective treatment for ulcerative colitis. Its effect is dose-related but so also are the side-effects, which are largely due to the sulphapyridine moiety. The active therapeutic
moiety is 5-aminosalicylic acid (5-ASA).

This study compares the efficacy of a large dose of 5-ASA (4 G) as a nightly retention enema with a hydrocortisone enema (100 mg). Eighty-six patients with mild or moderate attacks of ulcerative colitis were randomly allocated to each treatment group and the trial was performed 'double-blind'. Clinical, sigmoidoscopic, and histological assessment was made before entry into the trial and after 15 days of treatment.

For the 5-ASA group, the clinical, sigmoidoscopic, and histological responses were all significantly greater (p<0.0025) than for the hydrocortisone-treated patients (clinical response 41/44 vs 24/42; sigmoidoscopic response 41/44 vs 23/42; histological response 34/44 vs 15/42). No side-effects were observed in either group.

Topical 5-aminosalicylic acid may therefore have an important role in the management of active ulcerative colitis.

T8 Salt-losing ileostomy diarrhoea: long-term treatment with a glucose electrolyte solution

K Ward, B Murray, C Feighery, G Neale, and D G Weir (Department of Gastroenterology, Federated Dublin Voluntary Hospitals, and St James's Hospital, Dublin) Ileostomy patients with ileal resections are especially predisposed to salt-losing diarrhoea. This condition usually responds to codeine phosphate and NaCl tablets. Rarely patients fail to respond and are dependent on long-term parenteral salt supplementation.

Three patients with established ileostomies and extensive ileal resections were studied. Each had become hypotaemic. Initial treatment was the parenteral restoration of body sodium. After repletion, conventional oral therapy failed to maintain a normal sodium balance.

An oral glucose/electrolyte solution—50% Dioralyte and 50% modified Fortran solution—with a composition of Na 77 K 13 and dextrose 100 mmol/l and Caloreen (glucose polymer) 12-5 g/l has been used to restore and maintain sodium balance. Sodium balance has been studied with the solution given alone, with salt tablets, with Trisorbon and with a conventional low fat diet. Each regimen lasted seven days.

The daily sodium requirement was 200-250 mmol/day. With 1-2 L of solution restoration took five days. The urinary sodium/potassium ratio was the most sensitive indicator of sodium depletion. This was 0-3 before treatment and 2-5 during treatment. Outpatient maintenance on the regime has now been from six to 18 months. Attempts to wean patients back to conventional therapy have failed.

T9 Prospective randomised trial of oral prednisolone versus prednisolone enemas in acute exacerbations of distal ulcerative colitis

I F Pinder, R J Dickinson, I Hamilton, W S J Ruddell, M F Dixon, and A T R Axon (Gastroenterology Unit and Department of Pathology, The General Infirmary, Leeds) Local steroids are standard treatment for distal ulcerative colitis; however, up to 40% of enema dosage may be absorbed. We compared oral prednisolone 7-5 mg/day with prednisolone enemas at night.

Thirty-six patients with an exacerbation of distal colitis were randomly allocated to either oral prednisolone or prednisolone enemas. They were assessed before and after two weeks' treatment on the basis of their symptoms and sigmoidoscopy with rectal biopsy. If no improvement occurred at two weeks they were crossed-over to receive the other treatment.

Seven of 18 patients started on oral prednisolone improved compared with 14 of 18 started on enemas (p<0.05 Fisher's test). Of the 11 who did not improve on oral therapy, nine improved when changed to enemas, and three of four improved when changed from enemas to oral prednisolone. There was no improvement on either therapy in three patients.

Prednisolone enemas are more effective in the treatment of acute exacerbations of distal ulcerative colitis, despite being less convenient for the patient. It remains unclear as to whether they act purely locally or have a partially systemic effect.

T10 Plasma prednisolone levels with oral and intravenous administration in acute colitis

Louise Berghouse, P R Elliott, and J E Leonard-Jones (St Mark's Hospital, London) JUDY ENGLISH and V MARKS (Clinical Biochemistry Department, Surrey University, Guildford) Prednisolone, 60 mg daily intravenously, is believed to be more effective in the treatment of severe acute colitis than 40 mg daily given by mouth. Plasma prednisolone levels measured by radioimmunoassay have been compared in patients with acute colitis and healthy controls given these therapeutic regimes. After one dose of 40 mg by mouth, the mean peak level was 206±35 ng per ml (SEM) in six patients, 362±44 in six controls (p<0.01); the disappearance half-time was 300±24 and 138±36 minutes respectively (p<0.001). Prednisolone was given intravenously either as a bolus of 20 mg every eight hours or as a continuous infusion at a rate of 2-5 mg/min. At 30 minutes after a bolus of 20 mg the mean level was 986±35 ng/ml in six patients and 956±22 ng/ml in six controls (NS); the disappearance half-time was 90±35 minutes and 145±35 minutes respectively (p<0.01). During continuous infusion the mean plasma level was 308±38 ng/ml in eight patients. At 30 minutes after 20 mg intravenously the plasma level in patients was almost five times greater than the peak level after 40 mg orally (p<0.0005). The constant level during intravenous infusion was greater than the maximum level observed after the oral dose (p<0.01). These findings may explain the apparently greater therapeutic effectiveness of intravenous administration.

T11 Lactose malabsorption in Greek adults: correlation of small bowel transit time with the severity of lactose intolerance

S Ladas, J Papnikos, and G Arapakis (Introduced by G Sladen (Research Unit, Second Propaedeutic Department of Medicine of the Athens National University Evangelismos Hospital, Athens, Greece)) Because jejunal lactase levels do not correlate with the severity of symptoms in lactase malabsorbers, it has been postulated that the rapidity of small bowel transit (SBT) of the residual lactose bolus may contribute to the production of symptoms.

Using breath hydrogen analysis after a 50 g oral lactose load, we have investigated the prevalence of lactose malabsorption in 200 Greek adults and examined the relationship between symptoms and SBT. One hundred and fifty subjects had increased breath hydrogen concentrations (>20 ppm) after the lactose load. In these individuals peak breath hydrogen
concentration was inversely related to SBTT (r=0.063, t=6.854, p<0.001) and the severity of symptoms decreased with increasing SBTT. Lactose malabsorbers with diarrhoea (n: 90) during the lactose tolerance test had an SBTT 51±22 minutes (x±SD) which was significantly (p<0.001) shorter than the SBTT of patients with colicky pain, flatulence, and abdominal distension (74±30, n: 53) and both groups had significantly shorter SBTT than that of asymptomatic malabsorbers (n: 7, 115±21, p<0.001). Reducing the oral lactose load (12 instead of 50 g), SBTT increased five-fold and the overall incidence of diarrhoea and/or symptoms decreased dramatically.

We conclude that (1) the prevalence of lactose malabsorption among Greeks is 75%, and (2) symptom production in lactose malabsorbers is brought about by a rapid SBTT induced by the large osmotic load of the residual lactose bolus in the jejunum.

**T12**

Salivary and jejunal flora in the normal and contaminated small bowel

I HAMILTON, B WORSLEY, J G SHOEMITH, E M COOKE, AND A T R AXON (Gastroenterology Unit, The General Infirmary at Leeds and Department of Microbiology, University of Leeds, Leeds) The relevance of isolation of 'salivary' organisms from the jejunum, and the extent of contamination with saliva during sampling are unknown. We have compared salivary and jejunal bacterial flora in 22 patients with suspected small bowel bacterial overgrowth and eight controls.

Eleven patients had small bowel overgrowth as determined clinically and bacteriologically. The principal organisms cultured were 'faecal' in seven, but in four Gram-positive non-sporing rods (G+NSR) were predominant. These organisms had different characteristics from those in the saliva of each patient.

In some controls and patients without overgrowth G+NSR distinct from those in saliva were isolated in low numbers from the jejunum. In seven other subjects without overgrowth, organisms identical with those in the saliva were isolated, suggesting contamination of the sample. In three of these, coliform organisms were cultured in large numbers from both saliva and jejunum, and a false-positive diagnosis of small bowel colonisation might have been made without salivary culture.

Culture of both saliva and jejunal aspirate allows recognition of a jejunal flora which may be present in large numbers in small bowel bacterial overgrowth, and is essential to avoid mistaking salivary contamination of samples for true small bowel colonisation.

**T13**

Colon function in rural and urban populations of Turkey

H AKTAN, A OZDEN, E KESIM, AND A N SMITH (Department of Medicine, Hospital of the University of Ankara Medical School, Ankara; and Department of Clinical Surgery, University of Edinburgh, Western General Hospital, Edinburgh) Changes in bowel function, such as bulkier faeces, rapid transit, and a low intraluminal colonic pressure, have been described after the addition of fibre to the diet. Bowel function has been examined in two populations, a rural and an urban, living in Turkey, where the fibre intake of the rural group was 3-7 times that of the urban population. The stool weight, intestinal transit, and intraluminal pressure of 12 urban subjects were compared with those of 14 rural ones. The rural dry faecal weight, reflecting solids, was increased as well as the wet one (p<0.05). The mean transit in the rural group was 48.4 hours compared with 77.3 in the urban one (p<0.02). The motility indices were higher for basal, food, and prostigmine stimulation for the latter because of the wide range of cholinergically stimulated motility was significantly affected. The daily faecal calcium excretion, increased when the dietary fibre intake is high, was greater in the rural group. It would appear that colonic function is radically different in peoples of the same ethnic stock who live reasonably closely together but consume a diet which differs markedly in its fibre content.

**T14**

Unconjugated bilirubin solubilisation in model bile under varying physicochemical conditions. A model for the mechanism of solubilisation

M K DUTT, B MURRAY, AND R H P THOMPSON (From the Gastrointestinal Research Unit, Rayne Institute, St Thomas' Hospital, London) Unconjugated bilirubin (uBr) may seed cholesterol gallstones. uBr competes with cholesterol and calcium for mixed micelles but its solubilisation mechanism is unknown. We have measured its equilibrium solubility in model bile.

1. Two solubility maxima; pHS 4.5 and 7.4, suggest different apparent pKas for each carboxyl group (analogous to oxalic acid). At physiological pH (6-4-8-0) uBr is therefore probably mono-ionised.

2. uBr solubility rose with increasing lipid concentrations but plateaued between 5-10 g/dl (cf. gall bladder bile 8.25±2.62 g/dl lipids, mean±SD, n=16), subsequently falling.

From (1) uBr has amphiphatic properties at physiological pH with ionised and hydrophobic regions. Therefore, like lecithin, it might be solubilised between bile acid molecules, but (2) and (3) suggest sensitivity to decreasing intermicellar distance with increasing repulsion between negatively charged micelles. uBr, therefore, is probably held by adsorption on the micellar surface.

Physiological pH, lipid concentrations, and Ba:L ratios favour uBr solubilisation. The mechanism is completely different from cholesterol (held inside micelles) and probably less stable and more sensitive to changes of intermicellar phase contents—for example, Ca++, or micellar shape induced by intramicellar cholesterol.

Therefore uBr is probably easily precipitated and a likely nucleating factor.

**T15**

Use of high pressure liquid chromatography (HPLC) and radioimmunoassay to measure circulating forms of cholecystokins (CKK) in man

P N MATON, A CLARE SELDEN, AND V S CHADWICK (Department of Medicine, Royal Postgraduate Medical School, London) Radioimmunoassays (RIAs) for circulating CCKs have been limited by difficulties in raising antibodies of sufficient specificity and sensitivity. Our approach has been to separate peptides before RIA using HPLC. After separation
a non-specific antibody may be used to assay individual fractions from the chromatograph.

Blood samples from three volunteers obtained fasting and after oral fat (Prosperol) were taken into trasyloL-heparin, separated, acidified, and subjected to preparative HPLC. More than 99% of proteins as well as lipids and electrolytes passed through the column, while peptides were retained. These were then eluted using organic solvents and the fractions processed by analytical HPLC. Fractions were assayed with a CCK antibody cross-reacting with all bioactive forms of CCK and gastrins and also for gastrin immunoreactivity using a specific gastrin antibody.

We found that HPLC separated the various CCKs and recovery was 95%. There was no gastrin immunoreactivity in CCK 8 fractions but, in fractions containing CCK 33 a correction for gastrin immunoreactivity was necessary. In fasting subjects CCK 8 was undetectable and CCK 33 was 13 pmol/l. After oral fat CCK 8 concentrations rose to 41±3 pmol/l (range 27–58) and CCK 33 to 40±0 pmol/l (range 33–47). Peak levels of CCKs were achieved at 15–30 minutes and levels were still raised at 90 minutes.

Combined HPLC–RIA enables assay of multiple circulating forms of CCK in plasma without the need for region-specific antibodies.

T16
Codeine phosphate abolishes the pancreatic polypeptide response to oral fat

T E ADRIAN, N D CHRISTOFIDES, D J O’SHAUGHNESSY, L O UTTENTHAL, AND S R BLOOM (Department of Medicine, Royal Postgraduate Medical School, London) Recent studies have shown that postprandial secretion of peptidel is reduced after administration of morphine in man. Many patients are prescribed milder opiates such as codeine phosphate, in both hospital and general practice. However, the influence of such drugs on pancreatic release has not been investigated.

Plasma concentrations of pancreatic polypeptide were measured after ingestion of 140 g double cream in five healthy fasting subjects, on two occasions. On one day fat ingestion followed one hour after 30 mg codeine phosphate (intravenously) and on the other day no drug was given.

On the control day pancreatic polypeptide levels rose after cream from 28±3 pmol/l (mean±SEM) to a peak of 229±73 at 60 minutes. This postprandial response was completely abolished by codeine phosphate (basal 30±9, 60 minutes peak 34±8).

Thus codeine phosphate, which is commonly administered for cough, pain, and diarrhoea, has a profound effect on postprandial pancreatic polypeptide secretion.

T17
Effect of acute alcohol exposure on the perfused feline pancreas

M G ASHTON, D HUTSON, AND T SCRATCHERD (Department of Physiology, University of Sheffield, Sheffield) The perfused in vitro feline pancreas has been used to assess the effect of acute alcohol exposure on secretin stimulated secretion.

In initial experiments, there were no significant changes in the secretory parameters after exposure to alcohol of perfusate concentrations of up to 100 mM for periods up to 70 minutes. Alcohol appeared in the pancreatic juice in concentrations approaching that of the perfusate (approximately 88% of concentration of perfusate, r=0.98). In contrast, acetaldehyde caused a marked inhibition of secretion at lower concentrations—that is, 67.3% reduction at 75 mM. However these concentrations are not applicable to blood concentrations expected in man.

In other experiments, 0.1 M sucrose or creatine were used as inert probe molecules to assess the permeability of this preparation before and after exposure to alcohol (40 mM or 100 mM). Only after exposure to 100 mM alcohol (70 minutes) did the preparation seem significantly more permeable to the smaller molecule of creatine. However, these changes were subtle and were significant in only two of the three permeability parameters evaluated (p<0.05, n=10).

The significance of these results will be discussed, but it would seem unlikely that acute exposure to alcohol mediates any significant direct pathophysiological event relevant to the pathogenesis of alcoholic pancreatic diseases.

T18
Intrapulmonary fibrin deposition in experimental acute pancreatitis

A R BERRY, G C DAVIES, A M MILLAR, AND T V TAYLOR (University Department of Clinical Surgery and Departments of Pharmacy and Medical Physics, Royal Infirmary, Edinburgh) Pulmonary abnormalities contribute to the morbidity and mortality of acute pancreatitis. The pathogenesis of such changes remains unclear, thus precluding therapeutic improvements. We have previously reported to this society that decreased pulmonary compliance and increased lung weight occur in experimental acute pancreatitis in the rat and have suggested that these abnormalities are due to intrapulmonary fibrin deposition. Using an animal model we have studied pulmonary fibrin deposition using 125I fibrinogen injection in four groups of eight rats—a sham operation group, an untreated pancreatitis group, and pancreatitis groups given low dose heparin (150 IU/kg subcutaneously) or dextran 70 (2 ml intravenously).

A 22% increase in the percentage of fibrin deposition occurred in the pancreatitis group (1.72±0.25% (SD)) compared with the control group (1.38±0.19%, p<0.01). This was completely abolished by both heparin (1.33±0.15, p<0.01) and dextran (1.13±0.1%, p<0.001).

The percentage uptake per gram of lung tissue was raised in the pancreatitis group (1.07±0.18%/g) compared with controls (0.9±0.0% g, p<0.05). This increase was likewise abolished by heparin (0.77±0.06%/g, p<0.01) and diminished, though not significantly, by dextran (0.91±0.08%/g, p>0.05).

These results confirm that pulmonary damage in experimental acute pancreatitis is associated with intrapulmonary fibrin deposition. It is likely that the same situation exists in humans with acute pancreatitis, and heparin and dextran may be beneficial in these patients.
ment with pancreatic supplements. These observations suggested that a constituent of pancreatic juice, which is present in pancreatic extracts, limits copper absorption and thereby helps to regulate copper metabolism. Any copper absorbed in excess of requirements is disposed of in bile where copper is bound in a macro-molecular complex which is poorly absorbed.

To test this hypothesis we have measured the two-hour uptake of $^{64}$Cu (100 $\mu$g cupric acetate) from isolated duodeno-jejunal loops in anaesthetised pancreatic duct ligated rats. The absorption of $^{64}$Cu was $3.12\pm0.24\%$ (m±SEM, n=6) when the dose was mixed with pancreatic juice and $5.07\pm0.18\%$ (n=6) when mixed with a protein free solution of similar composition, pH and osmolarity (p<0.001). An artificial juice made up from dialysed pancreatic extract was equally active in inhibiting $^{64}$Cu absorption ($3.86\pm0.34\%$). Uptake of $^{64}$Cu from a bile-pancreatic juice mixture (2.68±0.26%, n=6) was not significantly less than from bile alone (3.19±0.19%).

A protein constituent of pancreatic juice limits copper absorption; a constituent in bile limits copper reabsorption—these secretions help to maintain copper homeostasis.

**T20**

Comparison of fluid phase and adsorption endocytosis in gall bladder epithelium

D Hopwood, S Coigll, R A B Wood, and G Milne (Departments of Pathology and Surgery, Ninewells Hospital and Medical School, Dundee) Associated with exocytosis, secretory granule membrane is inserted into the plasmalemma and subsequently cell membrane is retrieved, usually as vesicles, to keep the cell volume constant. We studied this process using the electron microscope in guinea-pig gall bladder in vivo, injecting cationised ferritin, which binds to the sialyl residues, as a marker for cell membranes and horse radish peroxidase to follow the endocytosed fluid phase vesicular contents, after exocytosis of mucous droplets.

Cationised ferritin binds rapidly to the cell membrane and undergoes lateral movement and endocytosis in vesicles within five minutes. The labelled vesicles move first to the lateral intercellular membrane, and thence to the Golgi zone where the label is incorporated into lysosomes. After three hours cationised ferritin is exocytosed through the basolateral cell membranes and accumulates by the basement membrane, before crossing over the next two hours.

Horse radish peroxidase is taken up rapidly into vesicles which empty into the lateral intercellular spaces by five minutes, the marker reaching the lamina propria by 30 minutes.

The retrieval of cell membrane shows one-trip mechanism in gall bladder. The rapid uptake of horse radish peroxidase demonstrates a pathway of moderate capacity for the uptake of bile components.

**T21**

Iron-binding glycoprotein receptors in human intestinal brush borders

T M Cox, M W O'Donnell, C R Voylcs, and C Smadja (Division of Gastroenterology, Departments of Medicine and Surgery, Royal Postgraduate Medical School, London) Many transport systems and binding moieties for essential nutrients have been localised to the intestinal brush border. Iron uptake studies employing mucosal specimens of human duodenum have suggested that iron transport across this membrane can be stimulated adaptively in conditions of iron deficiency and pathologically enhanced in idiopathic haemochromatosis. Accordingly, we have investigated iron uptake kinetics in human brush borders and used affinity techniques to explore the membrane receptor components involved.

Brush border membranes were purified from surgical specimens of normal proximal intestine, obtained at biliary diversion procedures. Membrane uptake of $^{59}$Fe ascorbate at 37°C, as determined by microfiltration, was time-dependent over 20 minutes; initial uptake showed saturation kinetics in the range 45-450 $\mu$M.

After five minutes’ incubation radio-

A J Batchelor and J E Compston (Gastrointestinal Research Unit, Rayne Institute, St Thomas’ Hospital London) The
cause of osteomalacia among Asian immigrants is unknown, but an association with high-extraction flour consumption is reported. Metabolic bone disease is also a complication of intestinal malabsorption. In both these situations, interruption of an enterohepatic circulation of 25-hydroxyvitamin D3 (25(OH)D3) may be a factor.

We have studied the plasma disappearance of tracer doses of radiolabelled 25(OH)D3 given intravenously to 13 healthy volunteers on normal and high fibre diets, and to nine patients with intestinal malabsorption. Plasma radioactivity was monitored for up to 30 days by liquid scintillation counting. Four days were allowed for distribution equilibrium to be attained and the subsequent slope of the plasma disappearance curve was used to calculate the elimination half-life.

The mean plasma elimination half-life in healthy subjects on normal diets was 27.5±2.1 (±SEM) days, compared with 19.2±1.7 days in the high fibre group (p<0.02) and 14.3±1.8 days in the patients with malabsorption (p<0.001).

These figures demonstrate significantly increased rates of elimination of 25(OH)D3-3H in both groups compared with normal, and provide some indirect evidence to support the suggestion that high fibre diets and intestinal malabsorption may predispose to vitamin D deficiency by interference with an enterohepatic circulation of 25(OH)D3.

T24
Intestinal absorption of maltotriose and a maltopentose-hexose mixture in man

B J M JONES, B E BROWN, AND D B A SILK
(Department of Gastroenterology, Central Middlesex Hospital, London) Recent perfusion data have suggested that the low MW products of luminal starch hydrolysis may confer, like maltose, a kinetic advantage on glucose absorption. The present study was therefore carried out to determine whether such a phenomenon exists for maltotriose and a purified oligosaccharide mixture containing a predominance of five and six glucose molecules.

Normal human volunteers were intubated with a double lumen perfusion tube with a proximal occlusive balloon. Twenty-five centimetre segments of jejunum were perfused with isotonic, isocaloric sugar-saline solutions, containing either (1) 46.5 mM maltotriose (G3), (2) the oligosaccharide mixture (G5–6), or (3) 140 mM glucose (G1).

Glucose absorption (mmol/h/25 cm±SEM) was faster from G3 (73.8±18.7) than from G1 (41.6±10.0, p<0.05, n=5). Glucose absorption from G5–6 (63.6±9.8) was also faster than from G1 (49.9±10.4, p<0.05, n=7) but similar to that from G3. The rates of hydrolysis of G3 and G5–6 were both similar to that of maltose as previously demonstrated.1,2

Maltotriose and oligosaccharides containing up to six glucose molecules thus confer a kinetic advantage on glucose absorption. These findings not only reflect the high affinity of brush border α-glucosamylase for oligosaccharides of up to six glucose units but highlight the advantageous relationship that must exist between this enzyme and the glucose carrier.

T25
Are the jejunal luminal contents always iso-osmolar?

S LADAS, F E T ISAACS, Y QURESHI, G MURPHY, AND G SLADEN (Gastroenterology Unit, Department of Medicine, Guy’s Hospital and Medical School, London) Since the study of Fordtran and Locklear (1966) it has generally been accepted that irrespective of meal osmolality luminal contents entering the jejunum are iso-osmolar (280–300 mosm/l).

There is little evidence, however, to support this view. We studied the effects of two liquid meals (A: 460, B: 350 mosm/l, marker: phenol red) on the osmolality, pH, and electrolyte concentrations of jejunal contents aspirated 10–20 cm beyond the ligament of Treitz in nine normal subjects.

After meal A (460 mosm/l) jejunal osmolality increased within 5 minutes from 283±13 (X±SD) to 316±22 mosm/l (p<0.01), peaked at 1½ hours to 360±20 (p<0.001), and returned to isotonicity at 3½ hours (287±12 mosm/l). Similar changes were observed after meal B (350 mosm/l): 273±3 (fasting) 328±18 mosm/l (14 hours; p<0.01).

After both meals (pH: 6.5), pH was stable (6.0–6.5 range) for three hours but at 3½ and five hours it fell to 5.6±0.3 and 5.3±0.6 (X±SD) (p<0.01) respectively.

Sodium concentration changes were similar for both meals (Na+: 59, 23 mmol/l). They decreased progressively from 123±4 mmol/l (X±SD; fasting) to 86±13 at 1½ hours (p<0.001) and returned to fasting levels at four hours (123±8 mosm/l).

After meal A (K+: 47 mmol/l) potassium concentrations increased from 6.5±0.5 mmol/l to 14.3±4 (p<0.001) at 1½ hours to return to fasting levels (6.8±1.1 mosm/l) at four hours. Meal B (K+: 18 mmol/l) caused less pronounced changes.

We conclude that hyperosmolality of jejunal contents occurs physiologically after ingestion of hyperosmolar liquid meals. The electrolyte composition of the contents reflects that of the meal. Equilibration between luminal contents and plasma is clearly incomplete in the upper jejunum after meals.

T26
Relationship between small bowel motility and migrating myoelectrical complexes by a common electrode

I R MORRIS, C F DARBY, P HAMMOND, AND I TAYLOR (Departments of Surgery and Bioengineering, University of Liverpool, Liverpool) Intestinal motility can be recorded by measuring changes in electrical resistance at the junction between an electrode and smooth muscle. Hence simultaneous recordings of myoelectrical activity and motility can be obtained from a common electrode and the relationship during migrating myoelectrical complexes studied.

Serosal electrodes were implanted at operation on to the small intestine of four dogs. Recordings were obtained, after recovery, with the dog at rest and fasting.

During phase III of the myoelectrical cycle, motility was seen as waves, varying little in shape or amplitude, in phase with the myoelectrical activity. In 88% of instances there was a shift in the baseline, suggesting a change in tone.

During phase II, motility coincided with irregular bursts of spikes. The amplitude of movement varied greatly but the maximum was usually greater than the phase III amplitude (median 1.7 times phase III amplitude).

In 50% of phase I periods observed, bursts of motility lasting 0.3–5 minutes (median 0.9 minutes), in which the amplitude of movement equalled that of phase III, were seen with associated spike activity.

These findings suggest that caution is needed in identifying the cyclic phases of motility without recording myoelectrical activity simultaneously.
T27 Chronic active hepatitis: how many patients need to be treated?

M PONZ DE LEON AND N CARULLI (Istituto di Clinica Medica II, Università di Modena, Italy) Patients with chronic active hepatitis (CAH) may benefit from treatment with corticosteroids. Koretz et al. have recently shown that when the clinical criteria for treatment, according to the published trials, are carefully taken into account the patients who meet these criteria represent only a small percentage of the overall population of patients with CAH. To check these conclusions we reviewed the clinical records of the patients with biopsy-proved CAH hospitalised in our unit to verify how many met the criteria.

Of 122 cases, 32 were excluded, mainly because of alcoholism. Of the remaining 90 patients only four (4.4%) met the biochemical criteria that define disease activity—that is SGOT > 10 times the upper normal limits or SGOT > five times and gammaglobulins > 3 g/dl. The remaining 86 patients (95.6%) had insufficiently raised transaminases and/or gammaglobulins to meet the criteria. This group was mainly males (83, 96%), predominantly middle-aged, 68-6% of whom were HBAg positive. Most of them (90%) were entirely symptom-free.

Our results confirm that the vast majority of patients with CAH do not meet the criteria that define the disease activity. Thus the real benefit of corticosteroids in most of the patients with CAH has to be proved, as the above-mentioned trials presumably dealt with a subgroup of patients with severe disease, who do not seem to be representative of the large majority of patients with CAH.

T28 High relapse rate after withdrawal of immunosuppressive drug therapy in patients with autoimmune chronic active hepatitis

J E HEGARTY, B PORTMANN, A L W F EDDLESTON, AND ROGER WILLIAMS (Liver Unit, King's College Hospital, London) The role of steroids and azathioprine in inducing and maintaining remission in patients with 'autoimmune' chronic active hepatitis (CAH) is well established. The optimal duration of maintenance immunosuppressive drug therapy in patients in whom biochemical and histological remission has been achieved is less clearly defined. We have therefore studied prospectively the effect of withdrawing steroid and azathioprine therapy in patients with a clearly established diagnosis of 'autoimmune' CAH in biochemical and histological remission. Thirty patients (21 women, nine men) with CAH for three--12 years who had been in biochemical and histological remission for two--11 years were studied. Criteria for treatment withdrawal included a normal AST for longer than 18 months and a histologically inactive liver biopsy in the six months before treatment withdrawal. Steroids and azathioprine were withdrawn over two--10 months and relapse defined as an increase in AST three times normal. Biochemical relapse occurred in 25 (82%) patients within four weeks (median nine weeks) of starting treatment withdrawal and this was confirmed histologically in all thirteen patients in whom histology was obtained. So far only five (18%) patients remain in biochemical remission 26--33 weeks after treatment withdrawal. Although re-institution of immunosuppressive therapy was followed by prompt biochemical resolution in 24 patients, one failed to respond and subsequently died. The high relapse rate in this study emphasizes the need for continued immunosuppressive drug therapy in patients with 'autoimmune' CAH.

T29 Carbohydrate intolerance in idiopathic haemochromatosis a feature of pancreatic or liver damage?

G SMITH-LAING, R G CHAPMAN, SHEILA SHERLOCK, AND O K FADER (Department of Medicine, Royal Free Hospital, London, and Hagedorn Research Laboratory, Gentofte, Denmark) The contribution of hepatic and pancreatic damage to diabetes in idiopathic haemochromatosis (IH) has been assessed in nine patients without cirrhosis (IH) and five patients with cirrhosis (IH+C). Plasma glucose, C-peptide, and insulin were measured during a 100 g oral glucose tolerance test and compared with 12 control subjects (C) by the F test. Fasting glucose was raised in IH and IH+C (IH 4.6±0.2 mmol/l; IH+C 6.1±0.9 mmol/l; C 3.4±0.1 mmol/l, p < 0.01) but subsequently was elevated in IH+C only. Seven patients had a diabetic GTT. Plasma C-peptide concentrations did not differ between groups and peaked at 90 minutes. Fasting plasma insulin was raised in IH+C and reduced in IH (IH+C 0.126±0.04 mmol/l; IH 0.062±0.01 mmol/l; C 0.084±0.01 mmol/l, p < 0.01). Subsequently insulin secretion in IH and IH+C was significantly lower than C at 30 minutes (p < 0.01) despite similar C-peptide concentrations and peaked 60 minutes after controls.

It has been demonstrated that in IH carbohydrate intolerance is markedly enhanced by the presence of cirrhosis, which causes insulin resistance; patients with cirrhosis display fasting hyperinsulinaemia; insulin secretion is both relatively deficient and delayed. We conclude that carbohydrate intolerance in IH results mainly from the development of cirrhosis rather than pancreatic damage. In addition, there may be an abnormality of proinsulin metabolism leading to delayed insulin secretion.

T30 Impaired monocyte insulin binding in cirrhosis

C O RECORD, M G BRAMBLE, J WHITTAKER, M PINIEWSKA, AND K G M ALBERTI (Gastroenterology Unit and Department of Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne) In cirrhosis normal fasting blood glucose and normal or impaired oral glucose tolerance are associated with high insulin concentrations, findings which have been attributed to liver damage and resistance to the action of insulin particularly in the periphery. In order to assess the importance of peripheral insulin resistance in the glucose intolerance of cirrhosis we have studied monocyte insulin receptor status in 18 patients with biopsy-confirmed cirrhosis.

Fasting blood glucose was similar in patients to that in controls (n = 19), but fasting insulin concentrations were significantly increased (20±2 compared with 9±3 mU/l; p < 0.005). Blood glucose and serum insulin concentrations were significantly increased (from 60 to 150 minutes and 90 to 150 minutes respectively) after glucose. Five patients showed diabetic glucose curves and in these insulin concentrations were higher than in the group as a whole. Specific insulin binding by monocytes was significantly...
decreased in cirrhotics (1.2 ± 0.1% compared with 1.7 ± 0.1% \( p < 0.01 \)), but in the subgroup of cirrhotics with diabetic glucose tolerance curves insulin binding was not significantly different from controls.

In cirrhosis peripheral insulin receptors appear to be decreased, but this is unlikely to be an important determinant of glucose intolerance, which appears to be primarily due to impaired hepatic retention of the glucose load and impaired hepatic inactivation of insulin.

### T31

**Plasma half-life of endogenous C-peptide, insulin, growth hormone, and glucagon in patients with chronic liver disease**

G Smith-Laing, Sheila Sherlock, O K Faber, and H Orskov (Department of Medicine, Royal Free Hospital, London; Hagedorn Research Laboratory, Gentofte, Denmark, and Arhus Kommunehospital, Arhus, Denmark) Raised plasma hormone concentrations in liver disease may result from an increased hormone production or decreased catabolism. High glucagon and growth hormone concentrations have been implicated as a cause of carbohydrate intolerance in cirrhosis. Plasma glucose, C-peptide, insulin, glucagon, and growth hormone response to an intravenous infusion of 30 g arginine followed by somatostatin 5 \( \mu \text{g/min} \) for 60 minutes has been measured in seven patients with liver disease and seven controls and plasma half-life (T\( _{1/2} \)) calculated for each hormone. Plasma glucose concentrations did not differ during the arginine infusion but were significantly raised in the cirrhotic group during the somatostatin infusion (\( r < 0.05 \)). Fasting and peak plasma C-peptide and insulin did not differ between groups but glucagon and growth hormone were significantly raised in cirrhotic patients throughout the study. During the somatostatin infusion all hormones fell in parallel in controls and cirrhotic patients but glucose fell significantly only in controls. Plasma T\( _{1/2} \) was similar for all the hormones except C-peptide, which was prolonged in cirrhosis (T\( _{1/2} \) control 12.3 ± 8 SEM 0.96 min; cirrhosis 17.3 ± 1.9 min, \( p < 0.025 \)).

It is suggested that insulin resistance in cirrhosis is independent of growth hormone and glucagon; raised growth hormone and glucagon in cirrhosis result from hypersecretion; C-peptide catabolism may be impaired in chronic liver disease.

### T32

**Charcoal haemoperfusion with PG1\textsubscript{2} infusion in fulminant hepatic failure in the importance of early perfusion**

A E S Gimson, S Braude, P J Mellon, M Davis, and R Williams (Liver Unit, King’s College Hospital, London) The platelet damage and hypotension associated with charcoal haemoperfusion which previously curtailed its use in fulminant hepatic failure (FHF) can be prevented by a continuous infusion of prostacyclin (PG1\textsubscript{2}), a platelet-protective prostaglandin. We report here the results of serial daily charcoal haemoperfusion with a PG1\textsubscript{2} infusion in 41 patients with FHF from viral hepatitis (12), paracetamol overdose (26), and other drugs (three). Among the 113 perfusions there were no significant platelet losses or hypotensive episodes. Conscious level improved in 18 patients and 17 (41%) survived to leave hospital. In 18 patients haemoperfusion was started earlier when signs of grade III encephalopathy first appeared. Although all subsequently progressed to grade IV over the next 24 hours, survival in this group was significantly better than those in whom treatment was delayed (61% and 26%, respectively, \( p < 0.05 \)). In the subgroup of 14 patients with paracetamol-induced FHF treated early results were even better with a 70% survival. The frequency with which cerebral oedema developed after the start of perfusion was lower in patients treated early than in those treated later (44.4% and 82.6%, respectively, \( p < 0.025 \)). These results demonstrate the safety of charcoal haemoperfusion when carried out with PG1\textsubscript{2} in patients with FHF and emphasise the importance of an early start to such therapy in improving survival.

### T33

**Biliary output in man is associated with a rise in plasma motilin**

T Svensberg, N D Christofides, M L Fitzpatrick, S R Bloom, and R B Weldon (Royal Postgraduate Medical School, Hammersmith Hospital, London) Animal studies suggest that motilin may regulate biliary output into the bowel. Fasting biliary output was assessed for 2½ hours in nine healthy subjects by hepatobiliary scanning. Output of bile into the duodenum was observed one to three times during each experiment (\( n = 17 \)) and was always associated with partial gall bladder emptying (27±3\% mean±SEM). There was a striking relation between output of bile into the bowel and fluctuations in plasma motilin in that a motilin increment (13±2 pmol/l 20 minutes after the start of bile output, \( p < 0.001 \)) paralleled the appearance of radioactivity in the duodenum. Oral water (7.5 ml/kg), known to cause motilin release, also affected the biliary tract. In five of seven subjects water caused gall bladder emptying (30±4\%) and output of activity into the bowel, and the time-activity curve of the duodenal area paralleled the rise in plasma motilin (23±4 pmol/l). In the remaining two subjects oral water neither caused gall bladder emptying nor motilin release. We conclude that, in man, gall bladder emptying occurs in the interdigestive state, that oral water causes biliary output, and that these events are associated with a rise in plasma motilin. Whether there is a causal relationship between biliary output and motilin release remains to be established.

### T34

**Dynamics of the enterohepatic circulation studied by gamma-labelled bile acid**

R P Jazwari, R M Kupper, S T Mellor, J H Payne, V R McCready, and T C Northfield (Department of Medicine, St George’s Hospital Medical School, and Department of Nuclear Medicine and Physics, Royal Marsden Hospital, London) Our objective was to examine the potential of a gamma-labelled bile acid selenium-75 taurohomoholic acid (SeHCAT) for defining the dynamics of the enterohepatic circulation. Five healthy volunteers were studied on two successive days using a gamma camera/computer system. 25 uCi SeHCAT was taken orally on day 1 with a standard meal. Bile acid recycling time was determined from first appearance of SeHCAT in the gall bladder and small intestinal transit time by the hydrogen breath test. On day 2 the fasting and postprandial distribution of the bile acid pool was determined. Simultaneous comparative measurements of gall bladder emptying of a non-absorbable biliary marker (\( ^{99m} \text{Tc-HIDA} \))...
were available. The SeHCAT curve was identical for the emptying phase, but then rose again, indicating gall bladder refilling. Mean bile acid recycling time was 62 minutes, compared with 195 minutes for small-intestinal transit time. A mean of 52% of the bile acid pool was in the gall bladder when fasting, but this fell to 17% during eating. We conclude that dynamic imaging with SeHCAT is a valuable non-invasive method for measuring bile acid recycling time, fasting and postprandial distribution of the bile acid pool, and gall bladder refilling during a meal.

T35
Effect of thyroid function on the hepatic metabolism of cholesterol and bile acids

P LORIA, N CARULLI, M PONZ DE LEON, F ZIRONI, R IORI, AND F PIGNATTI (Clinica Medica II, Universita di Modena, Italy) Among the factors regulating sterol metabolism, thyroid hormones have been shown to exert some activity, although the reported results are controversial. The purpose of our study was to investigate the effect of thyroid dysfunction on hepatic sterol metabolism and on cholesterol absorption in seven hyperthyroid and five hypothyroid patients the following parameters were investigated: bile acid kinetics and pool size, biliary and plasma lipids, cholesterol absorption, and small bowel transit time.

Hyperthyroid patients had a chenodeoxycholic acid (CDCA) turnover (half-life: 2:3±0.8 days, synthesis: 394±330 mg/day) significantly (p<0.01) faster than hypothyroid patients (5.8±1.5 days and 113±4.7 mg/day respectively). Both cholesterol absorption (22.3±6.0% of the given dose) and small bowel transit time (5.0±0.7 h) in hyperthyroidism were significantly reduced compared with those of hypothyroidism (39.2±10% and 9.5±1.0 h respectively). Bile of both hyperthyroid and hypothyroid patients was supersaturated with cholesterol, although the saturation index of the hyperthyroid (1.2±0.3) was lower than that of the hypothyroid (1.7±0.8). As expected, in hypothyroid patients lipoprotein cholesterol was increased, mainly in the LDL fraction.

Our data would suggest that the excess of thyroid function is associated with an increased degradation of cholesterol to bile acids and an impaired absorption of cholesterol compared with hypothyroidism. These changes may contribute to the alteration of plasma cholesterol levels observed in these patients.

T36
Serum chemotactic activity in chronic liver disease

I A RAJKOVIC, A G M YOUSIF-KADARU, R J WYKE, A L W F EDDLESTON, AND ROGER WILLIAMS (Liver Unit, King’s College Hospital, London) Alcoholism and cirrhosis are associated with increased susceptibility to bacterial infection. Defects in serum chemotactic activity in patients with alcoholic cirrhosis have previously been reported but only limited studies on patients with liver disease of other aetiologies have been conducted. We have compared serum chemotactic activity in alcoholic cirrhosis, chronic active hepatitis (CAH), and primary biliary cirrhosis (PBC), using a modified Boyden chamber.

Of 25 patients with alcoholic cirrhosis, 18 (72%) had significantly reduced serum chemotactic activity with a mean of 51±SD 23% of control value. Those with the serum defect had significantly higher levels of serum bilirubin, alkaline phosphatase, and aspartate aminotransferase and lower albumin, but the defect was not related to levels of serum complement or immunoglobulins. This defect was found in a significantly lower proportion (five (29%) p<0.02 of 17 patients with CAH and none of 13 with PBC, including six with cirrhosis. In CAH there was no significant difference in liver function tests between those with and those without the defect and its incidence was similar in those with and those without cirrhosis (two of nine and three of eight respectively).

This suggests that the aetiology of liver disease may govern the generation of serum chemotactic defects and hence susceptibility to infection.

T37
Close association between HLA-B8 and primary sclerosing cholangitis

R W CHAPMAN, Z VARGHESE, R GAUL, N KOKINON, G PATEL, AND SHEILA SHERLOCK (Departments of Medicine, Histopathology, and Nephrology, Royal Free Hospital, London). The aetiology of primary sclerosing cholangitis (PSC) is unknown, but it is closely associated with ulcerative colitis, which occurs in approximately two-thirds of patients with PSC. We have compared the HLA status of 25 patients with PSC (17 men, eight women) with a control group of 561 kidney donors. Fourteen patients (56%) also had ulcerative colitis. Tissue typing was performed using a microcytotoxicity assay. Liver biopsies were examined for piecemeal necrosis and serum immunoglobulins and autoantibodies were measured.

The frequency of HLA-B8 was markedly increased in PSC patients, 15/25 (60%), compared with controls 140/561 (25%) (χ²=15.1; p<0.001). HLA-B8 was found in eight patients with ulcerative colitis and six females. The frequency of HLA-B12 (2/25) was decreased in PSC patients compared with controls (170/561) (χ²= 5.7; p<0.02). Moderate piecemeal necrosis was seen in 30% of HLA-B8 positive and 10% of HLA-B8 negative patients (NS). Serum immunoglobulin IgM concentrations were raised in 36% of the patients and IgG in 16% but were not related to the presence of HLA-B8. Low titres of smooth muscle antibody were found in 24% and antinuclear factor in 52% but did not correspond to the presence of HLA-B8.

It appears that in patients with PSC, like autoimmune chronic active hepatitis, there is a disease susceptibility gene associated with the HLA-B8 locus of the major histocompatibility complex which may be modified by other factors such as ulcerative colitis.

T38
IgM anti-hepatitis-B core and other serological markers in fulminant hepatitis B

A E S GIMSON, R TEDDER, Y S WHITE, A L W F EDDLESTON, R WILLIAMS (Liver Unit, King’s College Hospital, London) and Department of Virology, Middlesex Hospital and Medical School, London) The pathogenesis of the fulminant course of hepatitis B virus (HBV) infection remains unclear, although increased hepatitis B surface antibody (anti-HBs) production with rapid clearance of hepatitis B surface antigen (HBsAg) have been implicated. In order to examine whether this represents an exaggerated immune response to a single antigen or is part of a wider heightened response to all HBV antigens we have investigated serological markers of HBV within nine days of the onset of jaundice in 30 patients with acute hepatitis B, of whom 17 developed
fulminant hepatic failure (FHF). Compared with those with an uncomplicated course, the fulminant group had lower levels of HBsAg (3589 ± 1388 and 37 846 ± 7694 ng/ml respectively, p<0.001), a lower incidence of the HBeAg (two of 17 and 12 of 13 respectively, p<0.001), and significantly higher IgM anti-HBc levels (855.2 ± 194.2 and 308.7 ± 70.2 units respectively, p<0.05). Anti-HBe or anti-HBs were already detectable at presentation in five patients with FHF but in none of those with uncomplicated courses. These results are consistent with enhanced humoral responses to all three HBV antigens in patients with fulminant hepatitis B. In addition, the finding of IgM anti-HBc in two cases in which HBsAg was negative by radio-immunoassay shows the importance of testing for this viral marker in the definitive diagnosis of fulminant hepatitis B.

T39
Comparative study of biliary secretion of labelled human dimeric and monomeric IgA in rats and man

J S DOOLEY, B J POTTER, H C THOMAS, AND SHEILA SHERLOCK (Department of Medicine, Royal Free Hospital, London) In the rat, dimeric immunoglobulin A (dIgA) is cleared from the systemic circulation into bile by vesicular transport through the hepatocyte. Whether such a transport system for dIgA is present in man is controversial. We have studied the fate of dIgA and monomeric IgA (mIgA) in six male Sprague-Dawley rats and in four patients, three with biliary drainage. Human dIgA and mIgA were prepared from myeloma serum, labelled with isotopes of iodine, and administered simultaneously intravenously. Serum, bile, and urine samples were collected and counted.

In the rats, the plasma disappearance of 131I-dIgA and 131I-mIgA were similar. Biliary recovery (percentage of total dose given) was 21-32% for 131I-dIgA and 3-0-4-6% for 131I-mIgA in eight hours. Urinary recoveries of the isotopes over this period were 14-27% and 25-49% respectively. In the four patients 131I-dIgA disappeared more rapidly from the plasma than 131I-mIgA. Biliary recovery (eight hour) of 131I-dIgA in three patients was 0-2-0-9% and that of 131I-mIgA 0-1-0-2% Urinary recovery (24 hours) was 25-37% for 131I-dIgA and 9-12% for 131I-mIgA.

In conclusion, after injection of a trace amount of labelled human myeloma dIgA in man, rapid transport into bile, as observed in the rat, did not occur. The difference in plasma disappearance of dIgA and mIgA in man remains unexplained.

PLENARY
P1—P8

P1 Coeliac disease and malignancy
CHRISTINE M SWINSON, G SLAVIN, E C COLES, AND C C BOOTH, on behalf of the MRC Coeliac Malignancy Working Party (Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex) Since November 1978 a national register of patients with coeliac disease and malignancy has been maintained at the Clinical Research Centre. Of 400 patients so far notified from throughout the United Kingdom 300 have histological evidence of jejunal villous atrophy and histologically proved malignancy. Of these patients, 194 have been analysed in detail. One hundred and one were men and 93 women. Two hundred and twelve malignancies have occurred, more than one occurring in 16 patients. The mean age at diagnosis of coeliac disease was 52 years, and of the first associated malignancy 56 years. There were 105 lymphomas (50%), 53 gastrointestinal cancers (25%), and 54 tumours in other sites (25%). The lymphomas affected principally the small intestine and were predominantly histiocytic in type. In both sexes the proportions of gastrointestinal cancers were more than expected by comparison with the general population and were principally adenocarcinomas of the upper small intestine. There was no significant difference between the proportion of lymphomas occurring in patients who had a favourable histological response to gluten withdrawal and those who did not. Thus in coeliac disease the lymphoma occurring is predominantly of histiocytic type, small intestinal adenocarcinomas occur, and malignancy may occur whether or not treatment with gluten withdrawal is instituted.

P2 Does the extent of distal clearance affect survival after radical anterior resection for carcinoma of the rectum?

W G POLLETT AND R J NICHOLLS (St Mark's Hospital, London) With increasing use of low anterior resection the length of rectum removed below the tumour is often less than the recommended 5-6 cm. It is important to know if this decreases the chance of cure.

Between 1963 and 1975, 354 patients survived radical restorative operations for a single rectal adenocarcinoma. The length of rectum below the tumour (measured on fixed pinned-out pathological specimens) was <2 cm in 59 patients (group 1), >2 <5 cm in 184 (group 2) and >5 in 111 (group 3). The Dukes classification, histological grade, and extent of local spread of the tumours were similar in the three groups.

Overall crude five-year survival rates for groups 1, 2, and 3 were 68, 68, and 67 respectively. Corresponding cancer specific death rates were 29, 25, and 28%. These rates were also similar in matching pathological subgroups of the three main groups. Of 16 observed or suspected local recurrences there were three in group 1 (5%), seven in group 2 (4%) and six in group 3 (5%). These results suggest that a margin <2 cm below a rectal carcinoma does not affect survival or local recurrence adversely.

P3 Prospective randomised trial of vitamin D, calcium gluconate, and microcrystalline hydroxyapatite compound in the treatment of cortical bone thinning in post-menopausal women with primary biliary cirrhosis

O EPSTEIN, Y KATO, R DICK, AND SHEILA SHERLOCK (Departments of Medicine and Radiology, Royal Free Hospital, London) Women with primary biliary cirrhosis develop accelerated cortical bone thinning which is most marked after the menopause. Denominisation is due to malabsorption of calcium, phosphate, and vitamin D, and oestrogen withdrawal. We have assessed the value of parenteral vitamin D3, calcium gluconate, and microcrystalline hydroxyapatite compound in the treatment of cortical bone thinning.

Fifty-one patients were randomised into an unsupplemented group, a group receiving calcium gluconate (40 mmol
calcium daily), and a group treated with MCHC (35 mmol calcium and 22 mmol phosphate daily). All patients received 100,000 IU vitamin D₃ monthly by injection.

Over a mean follow-up of 14 months there was no significant change in serum calcium or phosphate levels. Pre- and post-treatment radiographs of the second right metacarpal were measured at the metacarpal shaft midpoint to determine morphometric changes in cortical modelling (medullary width, cortical thickness, cortical area, and percent cortical area). Significant cortical bone loss occurred in the unsupplemented group owing mainly to increasing medullary width (P < 0.01). Cortical bone measurements were unchanged in the calcium gluconate group. The MCHC group showed a significant gain in cortical bone, manifested by an increase in cortical thickness (P < 0.02), cortical area (P < 0.02), and percent cortical area (P < 0.05).

This study indicates that, in postmenopausal women with PBC, calcium supplements prevent bone thinning and MCHC is probably the supplement of choice.

P4 Is forcible bag dilatation of the cardia of lasting benefit in achalasia?

I W FELLOWS, A L OLIVIE, AND M ATKINSON (University Hospital, Queen's Medical Centre, Nottingham) To assess the value of forcible dilatation, 46 patients with achalasia aged between 13 and 85, undergoing a total of 73 Rider-Moeller pneumatic dilatations, have been followed for up to five years. Dilatation was done under general anaesthesia and complications arose in only two patients; one sustained a rupture of the oesophagus requiring immediate surgery, and the other aspiration pneumonia. There were no deaths and gastro-oesophageal reflux was not a serious problem after the procedure. Thirty-two patients required a single dilatation, 13 between two and four, and one patient needed five dilatations. The need for further dilatation was significantly greater in the 16 patients aged under 45 years (15 dilatations in 19 patient years follow-up) than in the 30 aged 45 or more at the time of the initial dilatation (nine in 50 patient years follow-up), P < 0.001. The need for further dilatation was not related to the initial lower oesophageal sphincter pressure.

It is concluded that pneumatic bag dilatation is an effective and reasonably safe treatment for achalasia in the older patient.

P5 Effect of cimetidine on twenty-four-hour intragastric pH, bacterial flora and concentrations of nitrite and nitroso-compounds

J BARNARD, D W DARKIN, N J VINEY, Z AHMET, N F LIGHTFOOT, R H HUNT, AND G J MOUND-THOMPSON (Smith Kline and French Research, Welwyn, and the Royal Naval Hospital, Haslar) It has been suggested that raised intragastric pH is associated with increased growth of nitrate-reducing bacteria, increased concentrations of nitrite and nitroso-compounds, and consequently increased risk of gastric carcinoma.

The effects of cimetidine on the intragastric milieu were studied in eight healthy men, taking a representative, standardised diet, throughout 24 hours on three occasions—that is, before, at the end of two weeks' cimetidine 1 g/day, and two weeks' further treatment with 400 mg at night. Gastric juice was sampled half-hourly during the day and hourly overnight for measurement of pH, nitrite, and total and stable nitroso-compounds. Hourly samples from four subjects were examined for counts of total bacteria (aerobic and anaerobic), nitrate-reducing bacteria, and different species. Twenty-four-hour hydrogen ion concentrations were significantly decreased by both treatments (by 52-8%, P < 0.01, and 44-7%, P < 0.01). Neither nitrite nor total or nitrate-reducing bacteria increased significantly with pH. Isolated bacterial counts > 10⁵ occurred above pH 3, but intragastric colonisation did not occur; species detected were those commonly found in saliva, not enteric organisms. Concentrations of total nitroso-compounds fluctuated markedly in relation to meals and overnight, but were not correlated with pH, nitrate, or bacterial counts, or with cimetidine treatment.

In this study cimetidine treatment did not alter concentrations of nitroso-compounds in gastric juice.

P6 Hepatitis-B core antigen is a target for T-lymphocyte damage to hepatocytes in HBsAg positive chronic liver disease

M MONDELLI, G MILI-VERGANI, D VERGANI, A L W F EDDLESTON, R WILLIAMS (Liver Unit, King's College Hospital, London) T-lymphocytes reacting with HBsAg on the surface of infected hepatocytes are generally considered responsible for liver damage in hepatitis-B viral (HBV) infection, although there are no direct experimental observations to confirm or refute this hypothesis. The demonstration that T-lymphocytes from patients with HBsAg positive chronic liver disease (CLD) are cytotoxic for their own hepatocytes in vitro has provided an opportunity to determine directly the specificity of T-cell cytotoxicity. Antibodies to different HBV antigens have been added to the cytotoxicity assay to cover viral antigens on the target cells, thus blocking the cytotoxic effect of T-cells reacting specifically with those determinants. The addition of IgG from high-titre anti-HBs antisera had no effect on T-cell cytotoxicity in 12 patients with HBsAg positive CLD, while the same concentration of high-titre anti-HBC IgG significantly reduced cytotoxicity values (from 58% to 21%, P < 0.01) and completely blocked T-cell cytotoxicity in 10 of the 12 patients. Blocking was also observed with IgC from a serum containing both anti-HBC and anti-HBc antibodies. Control human IgG containing no antibodies to HBV determinants did not affect cytotoxicity.

These results suggest that hepatitis-B core antigen, probably expressed on the surface of infected hepatocytes, is a major target antigen for T-cell cytotoxicity in HBsAg positive CLD, whereas HBsAg does not seem to be relevant, at least in this in vitro system.

P7 Endotoxin activation of macrophages recently recruited into the liver could promote hepatocyte damage

A R TANNER AND R WRIGHT (Professorial Medical Unit, Southampton General Hospital) Endotoxin administration potentiates hepatocyte damage in many clinical and experimental situations. The precise mechanism is unknown, but the possibility that endotoxin might promote liver damage through macrophage activation has been investigated using rats injected with stilboestrol. This model demonstrates enhanced susceptibility to endotoxin administration.

Macrophages have been isolated from rat livers using pronase digestion. The
production of a lysosomal enzyme, n-acetyl-B-glucosaminidase (NAG), and a neutral proteinase, plasminogen activator (PA), by these cells in the presence or absence of endotoxin has been measured in vitro. The production of NAG by macrophages from normal livers was low (0.25±0.05 nmol substrate hydrolysed/μg cell protein/h) and uninfluenced by endotoxin exposure. Macrophages from stilboestrol injected rats showed levels of NAG production similar to normal. These levels increased significantly on exposure to endotoxin (0.46±0.07) units. Both of these macrophage populations showed increased levels of PA secretion after endotoxin exposure. As there is a twofold increase in the number of hepatic macrophages in the stilboestrol model the potential exposure of hepatocytes to macrophage proteolytic enzymes after endotoxin administration is many times the normal level. Thus, endotoxin may promote hepatocyte damage in this model through the activation of macrophages recently recruited into the liver.

P8 Digestive disturbances induced via the central nervous system
D G THOMPSON, E RICHESON, AND J R MALAGELADA (Gastroenterology Unit, Mayo Clinic, Rochester, USA) We have tested the hypothesis that stressful stimuli acting via the central nervous system can perturb normal gastrointestinal function by studying in nine volunteers the effect of pain induced by immersion of a hand in cold water. After gastroduodenal intubation and during phase II (irregular) fasting gastroduodenal motility subjects ingested a mixed liquid meal (200 cal, 240 ml). A test stimulus (hand in ice water) or control (hand in water or 37°C) was then applied for 20 minutes, the choice being randomly determined. After completion of meal emptying and return to fasting phase II motility, the study was repeated using the other stimulus.

Gastric volume, gastric secretion, and pancreatic trypsin output were measured by the double-marker technique. Serial blood pressure measurements provided an extra-intestinal index of stimulus response.

All subjects responded to the cold water with a rise in blood pressure (p<0.01). Cold pain consistently disrupted gut function compared with control stimulation, delaying gastric emptying (p<0.05) and altering the patterns of gastric acid and pancreatic trypsin secretion, both in a biphasic manner (p<0.05). A reduction in secretion occurred during the stress, followed by a post-stress rise. Somatic responses to stress thus include alterations in digestive function, a finding possibly relevant to the pathogenesis of functional gut disorders.

F2 Are all gliadins toxic in coeliac disease?
P D HOWDLE, P J CICLITIRA, F G SIMPSON, AND M S LOSOWSKY (Departments of Medicine, St James's University Hospital, Leeds, and Guy's Hospital and Medical School, London) It is generally believed that α-gliadin is the toxic wheat protein for coeliac patients, so much so that efforts have been directed at breeding wheat not containing α-gliadin, in the expectation that it would be non-toxic in coeliac disease. Other gliadin fractions have not been tested in vivo, but there is a suggestion from in vitro testing that α, β, and possibly γ gliadins are toxic, but not ω-gliadin.

We have prepared α, β, γ, and ω-gliadin and tested them and Frazer's fraction III in six controls, six untreated and six treated coeliac patients, using organ culture, as previously described. All gliadins were toxic to coeliac mucosa in vitro, α being the most and ω the least toxic. Although, owing to the separation techniques available, it is impossible to exclude some degree of cross-contamination of the fractions, it would seem that all may have toxicity, which is of clinical importance in coeliac tissue. This is the first report of the possibility of ω-gliadin being toxic.

We conclude that all gliadins must remain under suspicion as to their toxicity in coeliac disease until they are tested adequately in coeliac patients.

F3 Study of abnormalities in interdigestive motor activity in systemic sclerosis
W D REES, R LEIGH, AND L A TURNBERG (University Department of Medicine, Hope Hospital, Salford) The small intestine is involved in 40% of patients with scleroderma. This study attempts to clarify motor abnormalities in this disorder and examines responses to metoclopramide and bethanecol.

Fasting motor activity in antrum, duodenum, and proximal jejunum was recorded for six hours in eight controls (21–64 years), eight scleroderma without intestinal symptoms (21–60 years), and five patients with manifestations of small bowel scleroderma (46–70 years), using slowly perfused tubes connected to strain gauge transducers.

Normal interdigestive activity was
observed in controls and patients without intestinal involvement, but was absent in three patients with bowel sclerosis and contractions were reduced in amplitude and frequency in two. Differences in cycle number and duration were not statistically significant, but the motility index per cycle was significantly less (p < 0.02) in patients with intestinal involvement, compared with the other two groups (antrum: 181 ± 103, 760 ± 86, and 1116 ± 97 mm² in patients with intestinal involvement; without involvement; and controls respectively. Duodenum: 153 ± 101, 1425 ± 186, and 1055 ± 241 mm². Jejunum: 268 ± 131, 1166 ± 97, and 1105 ± 128 mm²). Metoclopramide (10 mg intravenously) or bethanechol (2.5 mg subcutaneously) increased motor activity in all groups, but the response was reduced in patients with intestinal involvement.

It is concluded that patients with small bowel scleroderma have abnormal inter-digestive motor activity and respond poorly to metoclopramide and bethanechol. These results help to clarify the motor disturbance in scleroderma.

F4 Lactoferrin levels in plasma of patients with pancreatic diseases
L Benini, R F Harvey, I Vantini, G Brocco, W Piubello, G Cavallini, A E Read, and L A Scuro (3rd Medical Clinic, University of Padua, Verona, and University Department of Medicine, Bristol) Lactoferrin is an iron-binding protein of uncertain function that is found in many biological fluids. Greatly increased levels of lactoferrin are found in pancreatic and duodenal juice of patients with chronic pancreatitis, but not of patients with pancreatic cancer. Although these findings are of considerable interest, suggesting a useful test for pancreatic disease, intubation is still required. We have therefore studied plasma levels of lactoferrin, using a sensitive radioimmunoassay, in 60 patients with chronic pancreatitis, eight patients with pancreatic cancer, and in control subjects.

Plasma lactoferrin levels were significantly raised in patients with chronic pancreatitis (range 0.9–5.2 ng/ml) compared with controls (range 0.9–1.7 ng/ml, p < 0.001), patients with pancreatic cancer having lower levels (range 0.2–0.9 ng/ml, p < 0.01). However, the ranges overlapped by about 50%. In view of this the molecular nature of the immunoreactive lactoferrin was studied by using gel chromatography on Sephadex G200. Several molecular forms were present—a high molecular weight form found in all subjects, derived from leucocytes, and (only in patients with chronic pancreatitis) two low-molecular-weight 'secretory' forms. These low-molecular-weight forms seem to be responsible for the rise in total levels of plasma lactoferrin in patients with chronic pancreatitis.

F5 Reproduction of functional abdominal pain by proximal gut distension
K J Moriarty and A M Dawson (St Bartholomew's Hospital, London) The irritable bowel syndrome is the most common diagnosis made in gastroenterological outpatients and yet little is known of its pathophysiology. It is often assumed to be mainly due to colonic dysfunction. Recently it has been demonstrated that pain caused by colonic distension in patients with functional abdominal pain often had bizarre localisation and referral patterns. In this condition it seemed possible that the proximal gut was also a trigger area for the production of pain which was not always to the classical midline site. We have thus extended our observations to balloon distension of the upper gastric gastro-intestinal tract.

Twenty-one patients (6M, 15F), aged 19–69 years, with chronic abdominal pain, which was not classically colonic, swallowed a tube incorporating a balloon and mercury bag. Eight patients had previously undergone 15 fruitless operations for the relief of pain. The balloon was inflated in the ileum, jejunum, duodeno-jejunal flexure, duodenum, stomach, and oesophagus. In 13 patients colonoscopy with insufflation of the attached balloon was also performed. The pain of 14 patients was reproduced by proximal gut distension. In three of these colonic insufflation also reproduced their pain. Colonscopic but not proximal gut distension reproduced the pain in three further patients.

Thus the whole of the gastrointestinal tract and not the colon alone has the potential to become 'tender' and to be the trigger site for causing functional abdominal pain.

F6 Symptom scores in dyspepsia
G P Crean, A D Beattie, W J Card, R J Holden, R P Knill-Jones, R W Lucas, and D Spiegelhalter (Diagnostic Methodology Research Unit, Gastrointestinal Centre, Southern General Hospital, Glasgow) Approximately 1000 patients have been seen in a dyspepsia clinic serviced by consultants using a structured questionnaire containing a maximum of 121 items of information concerning symptoms. Final diagnosis based on further investigation and clinical follow-up has been established in 93% of all patients seen.

The symptoms elicited have been analysed by the technique of logistic discrimination, such that a score can be attached to each symptom; scores can be aggregated, and the probability of a diagnosis can be read from a simple chart. The probabilities resulting from the use of this method are well calibrated—the values are precise rather than approximate.

Scores for individual symptoms of peptic ulcer, gastric cancer, gall stones, and alcohol-induced dyspepsia will be discussed. The scores exemplify common clinical experience, and demonstrate how powerful these symptoms may be. Diagnostic accuracy using these scores is similar to that of consultants. If the system were available in primary care it would seem that up to 40% of hospital referrals for dyspepsia might be unnecessary.

F7 Immunoglobulin E in ulcerative colitis and non-specific proctitis—studies with a monoclonal antibody
J Piris and D L Murdoch (Department of Pathology, University Medical School, Edinburgh) Immunocytochemical studies of immunoglobulin E in the rectal mucosa of patients with non-specific proctitis and ulcerative colitis have yielded conflicting results. The reports of marked increases in the numbers of IgE-containing plasma cells in these diseases have not been confirmed. Nevertheless, these findings led to the suggestion that the pathogenesis of these diseases may involve a locally occurring allergic reaction. The discrepancies in these findings may be explained by degrees of specificity of the anti-IgE sera used. Some commercial
anti-IgE sera tested by us showed cross-reactivity with IgA. A monoclonal antibody to IgE was used in this study to avoid the cross-reactivity associated with the conventional antisera.

A study of rectal biopsy specimens from 10 cases of non-specific proctitis and 10 cases of ulcerative colitis could demonstrate no significantly increased number of IgE-containing plasma cells when compared with normal controls. In our opinion the previous findings of increased numbers of IgE-containing plasma cells can be explained by the lack of specificity of the antisera used. The results of this study lend little support to the hypothesis that an allergic reaction is involved in these conditions.

F8
Mechanisms for fat malabsorption in the contaminated small bowel syndrome

CATRIONA L LITTLE, A B J SPEEKENBRINK, M HEALY, J DUNNE, E SWEENEY, C T KEANE, R R O'MOORE, AND D G WEIR (introduced by Dr D G Weir) (Departments of Medicine, Clinical Biochemistry, Bacteriology, and Pathology, Trinity College, Dublin) Bacterial deconjugation of bile acids with resultant defective, micellar solubilisation of lipid is the most frequently cited explanation of fat malabsorption in the contaminated small bowel syndrome (CSBS). Adequate micelle formation was present in three cases of CSBS with steatorrhoea. In this study 18 patients with steatorrhoea and bacterial contamination of the upper small intestine (USI) and eight controls were intubated. A doubly-labelled (14C) taurocholate, (14C tripalmitate) test meal was given and fat absorption monitored over a three-hour period both by measurement of serial serum chylomicron concentration and the percentage incorporation of free fatty acids (FFA) into micelles of the USI juice. The presence or absence of free bile acids (FBA) and mean and peak intestinal bile acids (IBA) levels were estimated. USI biopsy was obtained in four of the patients and seven control subjects. Chylomicron release was abnormal in 13 of 17 patients. Micellar solubilisation was normal in 15 patients yet 10 of these had FBA and four had peak and three had mean IBA below the normal range. Abnormal micellar solubilisation was present in three patients, one of whom had FBA and one had both mean and peak IBA below the normal range. Electron microscopy demonstrated mucosal damage in three of four patients. The results indicate that fat malabsorption in these patients was most likely to be in the mucosal absorptive phase rather than defective micelle formation.

F9
Jejunal volatile fatty acid content: a reliable indicator of small bowel overgrowth

B W WORSLEY, I HAMILTON, J G SHOESMITH, E M COOKE, AND A T R AXON (Department of Microbiology, University of Leeds, and Gastroenterology Unit, General Infirmary at Leeds) Many bacteriology laboratories now employ gas chromatographic determination of volatile fatty acids (VFA) in clinical material as direct evidence of infection, typically by anaerobes. The efficacy of this procedure as a routine alternative to detailed jejunal aspirate culture has been studied in 32 patients. In 12 patients with overgrowth jejunal aspirate yielded $>5 \times 10^4$ orgs/mL. Glucose hydrogen breath tests (GHBT) were positive in nine of 10 and 14-C-glycocholate breath tests in two of four. In 11 of these jejunal acetic acid concentration exceeded 0.3 mM and was grossly raised (mean 1.1 mM) if the bacterial count was greater than $10^7$/ml. Appreciable amounts of higher VFA were also a notable feature of this group. Jejunal aspirate in four of the remaining 20 patients was 'sterile', and in 16 yielded low or moderate counts comprising a simple or salivary flora. In five GHBT was positive albeit weak. VFA were undetected in 16, were present in trace amounts in three (<0.25 mM acetic), and exceeded 0.3 mM in only one. Grossly raised acetic acid levels, particularly with higher VFA, are a reliable indication of bacterial overgrowth.

F10
Indium-111 leucocyte scan in ulcerative and Crohn's colitis: a comparative study

D T STEIN, G M GRAY, M F ANDERSON, D A GOODWIN, AND, R MCDougall (Departments of Medicine and Radiology, Stanford University and Palo Alto Veterans Administration Medical Centers, Stanford, California) A prospective study comparing the indium-111 leucocyte scan to barium enema, colonoscopy, and/or surgery was completed in 15 patients with ulcerative (10) or Crohn's (five) colitis. Location of radionuclide uptake on indium scan was compared with location of disease at barium enema (13), colonoscopy (three), or surgery (two). Disease activity, as judged by intensity of radionuclide uptake, was compared with clinical grading of disease activity using the Crohn's Disease Activity Index for both forms of colitis. Scans and radiographs were read blindly and a numerical grading system was used to quantify the accuracy of the scan. Correlation between indium scan and other diagnostic studies was excellent in 12 cases, moderate in one, and poor in three. Activity of disease as assessed by the indium scan closely paralleled the clinical activity of disease. Disease activity was accurately predicted in 12 cases, underestimated in three, and overestimated in two. Two patients had indium scans during acute colitis and repeat scans when asymptomatic. In both cases radionuclide uptake in the colon decreased from universal colitis to no uptake. The indium-111 leucocyte scan provides an accurate non-invasive method for evaluating the extent and severity of inflammation in patients with ulcerative or Crohn's colitis.

F11
Changes in serum prolactin and sex hormones in patients on cimetidine therapy

C J OLIPHANT, C W VENABLES, ANN MCRAE, AND K G M M ALBERTI (Departments of Surgery and Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne) Previous acute studies with intravenous cimetidine have demonstrated a rise in serum prolactin. 'Gynecomastia occurs in a small proportion of patients taking cimetidine and it may be that subsequent changes in sex hormone levels account for this. The present study was thus undertaken to investigate change in serum prolactin and other sex hormones during oral cimetidine therapy.

Twenty-eight patients with endoscopically confirmed active ulceration (21 DU; seven GU) had blood samples taken for serum prolactin, testosterone, oestradiol, FSH, and LH at the time of diagnosis and after six weeks' therapy with cimetidine (1 g/day), at which point their ulcers were healed. Another group of patients on 'maintenance' therapy were assessed during follow-up. At diagnosis serum prolactin was raised in the majority.
patients ($\pm 137.8$). This fell in every case after treatment ($\pm 16.3$ mU/l). All were now within the normal range (upper limit 450 mU/l). There were no significant changes in any of the other sex hormones. Patients relapsing or controlled while on maintenance therapy usually had prolactins within the normal range.

This study demonstrates that serum prolactin is raised in patients with active ulceration and depressed by cimetidine treatment. Current studies are directed at determining whether this raised level is specific to peptic ulceration or is a stress reaction.

F12
Acid secretion in different stages of gastric carcinoma

F MISAKI and K KAWAI (introduced by P B Cotton) (Department of Preventive Medicine, Kyoto Prefectural University of Medicine, Japan) Differences in average age of presentation and some radiological studies suggest that it takes about 10 years for early carcinoma of the stomach to become advanced. We have measured preoperative gastric acid secretion in patients at different stages of carcinoma to study whether or not chronic gastritis with secretory deficit precedes the occurrence and growth of the neoplasm. The extent of the growth in 112 patients was divided on operation specimens: early gastric cancer within the mucosa (m) or the submucosa (sm), and advanced carcinoma extending into the muscle layer (pm) or the serosa (s). Maximal acid output (mao) decreased as the extent of the neoplasm became deeper: 8.01 ± 1.7 mEq/h in m-carcinoma, 6.05 ± 1.43 in sm-carcinoma, 6.22 ± 1.39 in pm-carcinoma, and 3.95 ± 0.82 in s-carcinoma. These results suggest that gastric carcinoma occurs and grows on the gastric mucosa with normal secretory capacity and that chronic gastritis may be a late occurrence in development of carcinoma. Patients with tubular adenocarcinoma showed lower mao (5.29 ± 1.98 mEq/h) than those (10.36 ± 2.92 mEq/h) with poorly or undifferentiated carcinoma in early cancer. This may simply reflect the higher average age of patients with tubular adenocarcinoma, which may occur on the mucosa with impaired secretion.

F13
The unnatural history of drug-associated gastric ulcers

M R THOMPSON (Department of Surgery, Bristol Royal Infirmary) In a review of 201 patients with gastric ulcers it was shown that patients taking a non-aspirin non-steroidal anti-inflammatory drug were mostly elderly women, the ulcers were usually chronic, had often bled, and gave rise to little dyspepsia. Thirty-seven such patients (10 men, 27 women) have now been studied further to determine their subsequent progress (mean 4.0 years) by sending their GPs questionnaires, reviewing their notes, and interviewing. Twenty-seven had chronic ulcers; seven acute ulcers (three not determined). Of 27 chronic ulcer patients (CUP) six had had surgery (five to stop bleeding) during the first hospital admission; in nine patients ulcer healing was confirmed and only three of these subsequently developed mild dyspepsia; in 12 CUP ulcer healing was not confirmed but only one developed severe dyspepsia and two mild dyspepsia. Four of six patients developing dyspepsia were again taking a non-steroidal anti-inflammatory drug (NAD). No patient has needed surgery or been definitely shown to have a second ulcer. Sixteen patients (16/35 = 46%) have subsequently been given NAD, seven of whom (7/16 = 43%) developed dyspepsia. It is concluded that drug-associated ulcers, unlike idopathic ulcers, tend not to recur and rarely if ever need surgical intervention for dyspepsia even though at least 43% continue to take NAD. This is further evidence that they are a distinct subgroup.

F14–F26
Cimetidine and the future

F14
Studies with H 168/68, a novel gastric acid secretion inhibitor

G EKVENED, E CARLSSON, C CEDERBERG, E FELLENIUS, U JUNGREN, H LARSSON, P LUNDBORG, A POTAGE, S E SJÖSTRAND, G SANDELL, B WALLMARK, U HAGLUND, R LETH, T LIND, AND L OLBE (introduced by J H BARON) (Research Laboratories, AB Hässle, S-431 83 Mölndal, Sweden, and Department of Surgery II, Sahlgren Hospital, Gothenburg, Sweden) Isolated guinea-pig gastric mucosa and isolated rabbit and human oxyntic glands produce acid in the presence of histamine, db-cAMP, and high K+ concentrations. Cimetidine blocks only the response to histamine. H 168/68, a substituted benzimidazole, blocks the response to all three secretagogues, suggesting a site of action peripheral to cimetidine. This may be the K+-dependent proton pump which has been found only at the secretory surface of the parietal cell, and, if so, H 168/68 offers a highly selective means of suppressing acid secretion.

Five healthy subjects each received four oral doses of H 168/68 randomised with placebo during pentagastrin (30 µg/h intravenously) stimulation tests. Peak inhibition of acid secretion was 46, 70, 95, and 100% with H 168/68 doses of 20, 40, 60, and 90 mg, respectively (20 mg = 58 µmol). Inhibition was maximal one to two hours after drug and persisted virtually unchanged for two to three hours. In another study in six subjects maximal acid secretion (pentagastrin 90 µg/h intravenously) remained depressed 24 and 48 hours after a dose of 20 mg, but returned to pretreatment levels by 72 hours. H 168/68 plasma concentrations peaked within 40 minutes, then declined with a half-life of about 50 minutes. H 168/68 produces long-lasting, dose-dependent inhibition of acid secretion in man.

F15
Effect of LM24056 in man on meal-stimulated gastric acid and serum gastrin responses

R W SPENCE, J M OLIVER, S M STOKES, M COOK (introduced by R F Harvey) (Department of Gastroenterology, Frenchay Hospital, Bristol) LM24056 is an inhibitor of gastric acid and pepsin secretion in animals and of pentagastrin-stimulated and overnight gastric secretion in man. Preliminary data indicated that this compound might also possess antigastrin activity. To investigate LM24056 further 16 healthy volunteers had an identical test 'lunch' (sieved oxtail soup plus Oxo) two hours after LM24056 200 mg or placebo tablets administered double-blind on two separate days. Twelve of the volunteers performed identical studies twice more after 100 mg and 50 mg doses. Intragastric pH was determined in 10 ml aliquots of gastric contents aspirated through a Ryle's tube introduced before...
the test meal. In venous blood samples plasma concentrations of LM24056 were measured and serum gastrins were estimated by radioimmunoassay (antibody affinity for gastrins G17-1 and G14-1). Hydrogen ion activity was significantly reduced in all gastric samples from the second and third test hours (p < 0.01 to < 0.05, paired t test) for the 100 mg and 200 mg doses (but not 50 mg) compared with placebo. Peak gastrin and integrated gastrin responses were significantly increased after 200 mg but not after the smaller doses (Wilcoxon matched pairs signed ranks test). Therefore LM24056 produces prolonged reduction of gastric acidity in man but does not suppress the gastrin response to a meal.

**F16** Comparison of prostaglandin E\(_2\) (PGE\(_2\)) and ranitidine in protection of gastric mucosal bleeding caused by aspirin in man

S J KONTUREK, N KWIĘCIEŃ, W OBTRUWIECZ, M POLANSKI, and J OLEKSY (Institute of Physiology, Medical Academy, Cracow, Poland) PGE\(_2\) given orally has been reported as preventing faecal blood loss caused by indomethacin or aspirin (ASA) in man, but it is unknown whether other inhibitory agents, particularly histamine H\(_2\)-receptor antagonists, have similar effects. This study was designed to compare the effects of oral administration of PGE\(_2\) in non-antisecretory dose (0.5 mg) and ranitidine, a new H\(_2\)-receptor antagonist, given orally in antisecretory (50 mg) or non-antisecretory dose (5 mg) on ASA-induced gastric microbleeding and DNA loss determined chemically in gastric washings in eight healthy subjects. The administration of PGE\(_2\), ranitidine, or placebo was followed 30 minutes later by 500 mg ASA given four times daily for two days. Blood and DNA losses in serial gastric washings were measured for 30 minutes and the results expressed as outputs per day. Normal gastric blood loss averaged 0.09 ml/day and DNA loss averaged 0.15 mg/day. ASA increased gastric bleeding to a mean of 1.96 ml/day and DNA loss to 2.14 mg/day. PGE\(_2\) or ranitidine administered in larger anti-secretory dose reduced the gastric microbleeding and DNA loss to the pretreatment level. Smaller non-antisecretory dose of ranitidine did not affect gastric bleeding and DNA loss. This study confirms that oral PGE\(_2\) has a protective action on gastric mucosa exposed to ASA and shows that ranitidine can also protect the mucosa against ASA injury, but this is probably due to the inhibition of gastric secretion.

**F17** Basal and peak acid outputs and intra-gastric acidity are reduced for 24 hours by a single daily dose of the histamine H\(_2\) receptor antagonist SK&F 93479

JANE G MILLS, K A JONSSON, ANNETTE CLANCY, G BODEMAR, DIANA VINCENT, B NORLANDER, A WALAN, R H HUNT, AND W L BURLAND (Smith Kline and French Research, Welwyn, the Royal Naval Hospital, Haslar, and the Departments of Clinical Pharmacology and Internal Medicine, University Hospital, 381 85 Linköping Sweden) In a previous study the anti-secretory effect of the H\(_2\) antagonist SK&F 93479 was shown to be prolonged and its potency (weight for weight) 12 times that of cimetidine.

Mean basal acid output (BAO) in a group of eight peptic ulcer patients was reduced from 1.9 mmol/l (pretreatment) by 100% and 77% two to three and 24-25 hours after a single oral dose of SK&F 93479 40 mg. In a separate group of eight patients BAO was reduced from 3.2 mmol/l by 86% and 38% at those times after a dose of SK&F 93479 25 mg.

Mean peak acid output, in response to subcutaneous pentagastrin 6 µg/kg was reduced from 33.4 mmol/l (pretreatment) by 70%, 48% and 28% in the 4th, 10th, and 26th hours after dosing in the first group and from 32.3 mmol/l by 54%, 24% and 17% in the second group. Peak plasma concentrations occurred two to four hours after dosing, mean 1.75 µg/ml after 40 mg, 0.97 µg/ml after 25 mg. Mean concentrations after 24 hours were 0.19 µg/ml and 0.11 µg/ml respectively.

In eight healthy subjects SK&F 93479 40 mg at night reduced mean hourly 24-hour hydrogen ion (H\(^+\)) activity from 35.6 (no treatment) to 13.8 mmol/l (61.2%, p < 0.05), 40 mg twice daily to 15.3 mmol/l (57%, p < 0.05), and cimetidine to 13.0 mmol/l (63.5%, p < 0.05). There were no differences between treatments. All treatments were most effective overnight; mean hourly H\(^+\) activity 2400 to 0700 was reduced by 68.2, 61.8, and 69.0% respectively. SK&F 93479 40 mg at night inhibited mean hourly H\(^+\) activity 0800 to 1300 the following morning by 56.1% (p < 0.05). Cimetidine was the most effective from 1400 to 1900 but the differences between treatments were not significant. The pharmacological response to SK&F 93479 40 mg at night measured in seven of the subjects was not modified by pre-treatment for seven days. These results confirm that SK&F 93479 is a potent and long-acting anti-secretory agent in man and suggest that a single night-time dose should be evaluated in patients with peptic ulcer disease.

**F18** Comparison between medical and surgical management in 220 cases of upper gastrointestinal haemorrhage

ALISON M LEAK, E L PALFREY, AND I D STRICKLAND (Kingston Hospital, Kingston upon Thames) As an agreed hospital policy, patients with upper gastrointestinal haemorrhage were admitted by physicians for six months of the year and by surgeons for the other six months. All 220 patients admitted over a two-year period were included, and 'medical' and 'surgical' groups were well matched for age and sex. Ten patients were readmitted with a further bleed during this study.

When treated conservatively, the medical group was kept in hospital for a longer period and transfused more blood than the surgical group. 111 patients were endoscoped and the diagnostic rate was 72%. Early endoscopy did not increase the diagnostic yield. Significantly more surgical admissions were operated on than medical admissions, particularly when only the peptic ulcer patients were considered (χ\(^2\)=11.47, p < 0.01).

Fourteen patients in each group died. Six were severely shocked, dying shortly after admission, and another 12 could be classified as unavoidable deaths. Only five patients with diagnosed peptic ulcers died and four of these were after partial gastrectomy. Our postoperative mortality of 16% compared with an overall peptic ulcer mortality of 5% suggests that conservative management may often be desirable, but the outcome of these two groups of patients is under further study.

**F19** Ranitidine in acute upper gastrointestinal haemorrhage

J DAWSON AND R COCKEL (Selly Oak Hospital, Birmingham) Recurrent bleeding in acute upper gastrointestinal
haemorrhage continues to be associated with significant morbidity and mortality despite early hopes that cimetidine might be beneficial. Ranitidine, a more potent gastric-acid inhibitor, might perhaps be more effective. This double-blind study compares the effect of 10 day ranitidine (150 mg thrice daily) with placebo in 114 consecutive patients presenting to a district hospital with acute upper gastrointestinal haemorrhage. Patients were endoscoped within 24 hours. One hundred and nine completed the study, 55 receiving ranitidine and 54 placebo. The groups were similar for age, shock, haemoglobin, and transfusion requirement.

Rebleeding occurred in 20 patients (18%), seven on ranitidine (13%), and 13 on placebo (24%). Duodenal ulcers were favourably influenced by ranitidine (two rebleeds in 21 patients) compared with placebo (six in 20). There was no difference in gastric ulcer (3/10 rebleeds on ranitidine, 2/8 on placebo). There were no rebleeds in oesophagitis (ranitidine five patients, placebo eight). One patient re-bled in both ranitidine (11) and placebo (five) groups of patients with gastritis or duodenitis. In the remaining assorted lesions one rebleed occurred on ranitidine (eight) and four rebleeds on placebo (13). These results indicate a trend towards a favourable effect of ranitidine particularly in duodenal ulcer and justify its continuing assessment in acute gastrointestinal bleeding.

F20
Trial of cimetidine, tranexamic acid and placebo in the management of acute upper gastrointestinal haemorrhage

A L OGLIVIE, D BARER, M W DRONFIELD, M J S LANGMAN, M ATKINSON (University Hospital, and Department of Therapeutics, City Hospital, Nottingham) Five hundred and thirty-two patients with a diagnosis of acute upper gastrointestinal bleeding were randomly allocated to receive cimetidine, tranexamic acid, or placebo in a prospective double-blind study. Sixty-four patients were subsequently withdrawn, and a definitive diagnosis was not reached in 54 patients. Of the remaining, 142 patients received cimetidine, 138 tranexamic acid, and 134 placebo.

The numbers of operations (cimetidine, 19; tranexamic acid, 28; placebo, 21), incidence of rebleeding (cimetidine, 19; tranexamic acid, 24; placebo, 24) and average transfusion requirements were not reduced by active treatment. There were fewer deaths in the tranexamic acid group (5) (p<0.02) than in the placebo group (16) owing to a smaller postoperative mortality (p<0.05). In the cimetidine group the death rate (11) did not differ significantly from placebo.

Two hundred and eighty-seven patients had chronic peptic ulcers (144 duodenal ulcers; 143 gastric ulcers). Analysis of the ulcer patients as a whole or separately showed no difference in operation rates, mortality rate, or transfusion requirements between treatments. In patients with gastric ulcers, cimetidine was associated with a lower incidence of rebleeding than tranexamic acid (p<0.05), but not placebo.

We would seem that neither cimetidine nor tranexamic acid confers any advantage in the management of patients with acute upper gastrointestinal haemorrhage.

F21
Cimetidine versus surgery for recurrent ulcer after gastric ulcer

S K LAM, J KOO, AND G BONG (Combined Gastrointestinal Unit, University Department of Medicine and Surgery, Queen Mary Hospital, Hong Kong) The efficacy of cimetidine versus surgery in the treatment of recurrent ulcers after definitive surgery for chronic duodenal ulcer was evaluated in two groups (23 each) of patients comparable in age, sex, symptom duration before primary operation, interval between recurrence, symptoms of recurrence, habits, nature of primary operation, ulcer site and size, and gastric acid secretion, basal and after insulin and pentagastrin. Cimetidine 1 g daily healed 79% and 91-6% of recurrent ulcers, as assessed endoscopically, after six and 12 weeks respectively. Eighteen of 22 patients (two defaulted, two at six and 10 months only) with healed ulcer completed one year maintenance treatment with cimetidine (400 mg at night). Maintenance cimetidine prevented relapse in 87-5%, while surgery was successful in 92-7% (p>0.1). The cimetidine group experienced significantly (p<0.02) fewer side-effects than the surgical group, with respectively 10% and 48% of patients having Visick grade II and above. After one year of maintenance treatment, cimetidine was withdrawn and ulcer recurred in 81-8% within six months. The relapse rates between the two groups were significantly different by life-table analysis (p<0.01). We conclude that cimetidine was as effective as surgery in preventing relapse of post-surgical recurrent ulcers and had fewer side-effects, but indefinitely prolonged therapy appeared necessary.

F22
Effect of cimetidine on peptic ulcer surgery in the north-west of England

C PRICE AND J B ELDER (University Department of Surgery, Manchester Royal Infirmary) After the introduction of H2-receptor blockade a massive reduction in gastroduodenal surgery was prophesied. The aim of this study was to analyse data for individual gastroduodenal operations over 12 years in the north-west region of England from 1974 to 1980. The frequencies of six operative procedures since the introduction of cimetidine in 1976 have been studied and compared with those in the pre-cimetidine era. Using mean quarterly figures the results for (a) 1977–8 and (b) 1979–80 were compared with those for 1974–6 and expressed as ratios: Billroth I partial gastrectomy (a) 1·05 (b) 0·88; Polyga partial gastrectomy (a) 0·84 (b) 0·73; vagotomy (all types) and pyloroplasty (a) 0·85 (b) 0·91; vagotomy and gastroenterostomy (a) 0·73 (b) 0·63; repair of perforated gastric ulcer (a) 1·23 (b) 1·5; repair of perforated duodenal ulcer (a) 1·07 (b) 1·49. Applying a 2-tailed t test at p<0·05, there has been no significant change in the frequency of Billroth I or vagotomy and pyloroplasty procedures. There was a significant decrease in Polya partial gastrectomies for 1979–80 and in vagotomy and gastroenterostomy procedures for 1977–8 and for 1979–80. There has been a significant increase in operations for repair of perforations of both gastric and duodenal ulcers for 1979–80. The advent of H2 blockers has had little effect on elective ulcer surgery but perforations have apparently increased in the north-west of England.

F23
Low dose cimetidine maintenance treatment in duodenal ulcer: intermediate term results

K D BARDHAN, J BERESFORD, AND R F C HINCLiffe (District General Hospital, Rotherham, and Smith-Kline and French, Welwyn) Low dose maintenance treat-
F24 What happens to duodenal ulcers that do not respond quickly to cimetidine?

K D BARDHAN (District General Hospital, Rotherham) On cimetidine 1 g daily 80% of duodenal ulcers (DU) healed within one month and 93% within three months. But in 70 patients (excluding those with Zollinger-Ellison syndrome) healing was delayed; they are considered to have a refractory duodenal ulcer. Forty-one patients eventually healed but after a mean treatment period of 6-9 months; but 28 patients did not, despite treatment for 9-4 months. In 48 patients the dose of cimetidine was increased to 2 g (31 healed) and in eight patients to 3 g (four healed). Twenty-one patients required admission on 27 occasions because of severe symptoms despite treatment; 11 patients had surgery but in two the ulcer recurred.

The cause of refractory duodenal ulcer is unknown. Such patients had only slight differences in clinical and endoscopic features compared with non-refractory patients; acid and pepsin output was similar; gastrin levels were normal; and preliminary evidence shows that there is no failure to inhibit acid secretion on cimetidine. A refractory episode can occur at any time; though earlier attacks responded swiftly to cimetidine, subsequent relapses are also usually refractory. The clinical significance is that it generally indicates the development of an increased virulence of the disease and a worsening of the prognosis.

F25 Cimetidine and perforated peptic ulcers

A J MCKAY AND C S MCARDE (University Department of Surgery, Royal Infirmary, Glasgow) Cimetidine is thought to have accelerated the previously noted reduction in elective peptic ulcer surgery, but its effect on the incidence of perforated peptic ulcers has not been reported.

A 15-year (1966-80) review of peptic ulcer surgery in a district general hospital is presented. Since cimetidine became available (November 1976) the mean annual number of elective operations has fallen from 40-6 to 36-5 (10%) reduction.

One hundred and five patients (78 male, 27 female; M: F 2:9:1) treated for perforation (97 duodenal, eight gastric) from 1978-80 were reviewed individually. Forty-one had an acute ulcer and 64 a chronic ulcer, eight of whom were taking cimetidine when they perforated and eight others had been on the drug previously.

Cimetidine has reduced elective peptic ulcer surgery. There has been no equivalent reduction in the incidence of perforation. It appears that cimetidine can relieve dyspepsia yet fail to protect from perforation. These findings should be taken in consideration in the evaluation of the role of cimetidine in the management of chronic peptic ulcer disease.

F26 Failure of maintenance therapy in duodenal ulcer

E J S BOYD, J A WILSON, AND K G WORMSLEY (Department of Therapeutics, University of Dundee) Ranitidine was given at night (150 mg) to 101 patients with duodenal ulcer for six months or more to prevent ulcer relapse. Patients were endoscoped after six months' and 12 months' treatment, or if symptoms recurred. Compliance was monitored by tablet counts and measurement of drug metabolites in early morning urine specimens.

Twenty-six patients (55%) remained free of recurrence after 12 months. There was no difference between patients with and without recurrence as regards age, sex distribution, duration of history, smoking habits, or alcohol consumption.

F27 Gastric fundic control of jejunal absorption

SUZANNE RHINNO-BARDMA, K BURD, J BLEDER, AND NJ ANDREWS (Departments of Surgery and Medical Biochemistry, University of Manchester) Recent work strongly suggests the existence in gastric fundic mucosa of a novel peptide which decreases absorption from the antrum and jejunum. Alkalisation and distension of the gastric fundus reduced absorption as did a porcine fundic mucosal extract. Can fundic distension alone initiate the response? Is the mechanism uniquely located in the gastric fundic mucosa? Four to 10 cm loops of proximal rat jejunum were perfused for 60 min with 0.15 M NaCl containing 10 mM glucose (n=50) or Te^{99m} (n=20) as absorption indicators. Perfusions (glucose n=8, Te^{99m}, n=4) were performed when the gastric fundus was distended with 3 ml air. In both control and test procedures the pH of the fundic mucosa was <4.

Gastric fundic distension decreased luminal loss of glucose by 28% (p<0.01) and absorption of Te^{99m} by 22%.
(p < 0.005). Low molecular weight peptide extracts of fresh porcine antral and jejunal mucosa, liver, lung, and brain infused via IVC in this bioassay did not inhibit glucose absorption, nor did infusion of known gastrointestinal peptides. A gastric fundic mucosal extract inhibited absorption of tracer by 47% (p < 0.0001, n = 8). We conclude that gastric fundic distension alone without alkalinisation reduces jejunal absorption and it appears that the factor responsible resides exclusively in the gastric fundic mucosa.

F28 Response of the lower oesophageal sphincter to increased intra-abdominal pressure: a vagally mediated mechanism

A L OGLIVE and M ATKINSON (University Hospital, Queen's Medical Centre, Nottingham) Lower oesophageal sphincter pressure (LOSP) has been shown to rise in response to increasing intra-abdominal pressure, but it is uncertain if this is a sphincter response or a purely mechanical phenomenon. LOSP was measured using a perfused triple lumen tube by the rapid pull-through method during rise in intra-abdominal pressure brought about by increasing the pressure, in increments of 10 mmHg, in a thigh sphygmomanometer cuff bound to the anterior abdominal wall. In 15 controls increasing intra-abdominal pressure resulted in a sustained rise in LOSP that was significantly higher than the resting level (p < 0.01). In six of these controls atropine resulted in a small decrease in resting LOSP, and increasing intra-abdominal pressure produced no significant rise above basal level. In six patients who had previously undergone truncal vagotomy resting LOSP was slightly lower than in controls, and there was no rise in LOSP with increasing intra-abdominal pressure.

These findings suggest that the response of the lower oesophageal sphincter to increased intra-abdominal pressure is a true sphincter response which is mediated by a vagal mechanism and that the test provides a valid means of assessing vagal function in the upper alimentary tract.

F29 Effects of alcohol on post-prandial functions in man

A CORTOT, G JOBIN, C AYMES, V GIRAUDEAUX, R MODIGLIANI (introduced by J C Rambaud) (Research Unit on Pathophysiology of Digestion, Hospital Saint-Lazare, Paris) The effects of ethanol on postprandial secretory and motor functions of the upper GI tract have never been assessed adequately. Therefore we measured by an intubation method, the influence of alcohol given with a meal on gastric emptying and secretion and pancreatic secretion. Four volunteers ate a homogenised meal (+14C-PEG) without (meal A) or with (meal B) ethanol (1 g/kg/bw) on two successive days. PEG 4000 in saline was perfused into the duodenum and gastric and jejunal (angle of Treitz) contents were sampled during five hours after eating. All samples were analysed for markers and ethanol; H+ ions were titrated in gastric samples and lipase in jejunal samples. Meal B emptied more slowly than A, the difference being maximum during the first two hours (respectively 143 ± 15 vs 227 ± 16 ml emptied, mean ± SE, p < 0.01). Gastric secretory and acid output and gastric acid delivered to the duodenum were not influenced by alcohol. Lipase outputs were higher after meal B during the fifth postprandial hour (158 ± 25 vs 101 ± 31, K IU, p < 0.05). Meanwhile alcohol was mainly absorbed in the stomach (61 ± 9 ± 3-6%), then in the duodenum (31 ± 3 ± 3-4%), resulting in minimal arrival of alcohol in the jejunum. Alcohol taken with a meal delays gastric emptying and maintains longer a significant pancreatic secretion while most of the ingested ethanol is absorbed before the angle of Treitz.

F30 Inhibition of gastric acid secretion by fenotimine, a new antisecretory agent

J G WILLIAMS, R J ROBERTSON, G J MILTON-THOMPSON, A HOLMANN, U DIETRICH, W REINHART, and F HALTER (Department of Medicine, Royal Naval Hospital, Plymouth, and Gastrointestinal Unit, University Hospital, Inselspital, Berne) Fenotimine is a new antisecretory agent. The mode of action is not known, but the compound appears in animals to be devoid of significant anticholinergic or H2-antagonist activity. The duration of action is prolonged, significant antisecretory activity being detectable in animals 24 hours after oral dosing.

We studied the effect of three doses of fenotimine (50, 150, and 250 mg) on food-stimulated acid secretion in six normal volunteers. Mean cumulative acid secretion at two hours after the meal (four hours after oral dosing) was 82.6 mmol following placebo. This was reduced by 29% (to 58.9 mmol) after fenotimine 50 mg (p < 0.01); 43% (46-7 mmol) after 150 mg (p < 0.01); and 47% (43.8 mmol) after 250 mg (p < 0.002). Duration of action was studied in eight normal volunteers. Each received a standard pentagastrin test on four occasions: eight and 12 hours after fenotimine 250 mg and eight and 12 hours after placebo, in randomised order. Compared with placebo mean acid secretion (mmol/hour) fell from 21.61 to 19.5 (p < 0.01) when tested 12 hours after dosing, and from 22.01 to 15.27 (30.5%) after placebo eight hours after dosing.

We conclude that fenotimine is a potent antisecretory agent with significant inhibition occurring at least eight hours after dosing.

F31 Enkephalin inhibition of vagally stimulated gastric and pancreatic secretion in men and dogs

S J KONTUREK, J JAWOREK, M CIESZKOWSKI, A V SCHALLY, and D H COY (Institute of Physiology, Medical Academy, Cracow, and Veterans Administration Hospital, New Orleans) Enkephalins have been detected in the vagal nerves and neurons of myenteric plexus but little is known about their action on vagally stimulated gastric and pancreatic secretion. In this study we infused intravenously D-Ala2-enkephalin (Enk), a stable enkephalin analog (40 μg/kg/h) alone or in combination with naloxone (40 μg/kg/h), a pure opiate antagonist, 30 minutes before, during, and 90 minutes after vagal stimulation induced in five healthy subjects by modified sham-feeding and in four dogs with oesophageal, gastric, and pancreatic fistulas by ordinary sham-feeding performed during 15 minutes. In men and dogs vagal stimulation increased H+ secretion, averaging respectively about 62 and 90% of the pentagastrin-induced maximal H+ output, and was accompanied by a significant (p < 0.05) increment in serum gastrin by 23 ± 5 μmol/l in dogs but not in men. Pancreatic protein outputs in men and dogs rose to peaks of about 72 and 86% of CCK maximum and was accompanied by a significant increment in serum pancreatic polypeptide (PP) level by 45 ± 6 and 29 ± 5 μmol/l, respectively.
Enk reduced the modified sham-feeding induced mean peak H⁺ output from 8·65±1·93 to 4·26±0·9 mmol/30 minutes in men and from 10·26±2·43 to 3·66±1·03 mmol/30 minutes in dogs. Peak pancreatic protein response to vagal stimulation was decreased from 790±165 to 426±107 mg/30 minutes in men and from 867±185 to 668±125 mg/30 minutes in dogs. Serum gastrin level was not affected by Enk but PP response was significantly suppressed in both species. The addition of naloxone to intravenous Enk infusion did not reverse the Enk-induced inhibition of gastric or pancreatic responses to vagal stimulation. We conclude that Enk inhibits gastric H⁺ and pancreatic protein secretion and suppresses serum PP response to cephalic stimulation both in man and dog and this effect does not seem to be mediated by specific opiate receptors.

F32 Does the human pylorus close in response to an isolated duodenal cap contraction? Studies with a new technique

G E LINHARDT, P ROBINSON, R H SMALLWOOD, AND A G JOHNSON (University Surgical Unit and Department of Medical Physics, Royal Hallamshire Hospital, Sheffield) Although during gastric emptying the pylorus closes with a terminal antral contraction, the key question for the prevention of duodenogastric reflux is whether the pylorus closes in response to a duodenal contraction when the antrum is relaxed.

We have studied the timing of pyloric closure using four silver wire electrodes 6 mm long mounted around the circumference of a Fogarty catheter (14-2 mm diameter) just proximal to the balloon. Impedance between opposite pairs of electrodes is measured at 100 KHz using a current of 100 μA. Pyloric closure is registered when all four electrodes are touched by the pyloric ring. The device is passed down the ACMI twin-channel gastroscope and positioned with the balloon just in the duodenum maintaining the electrode in the pyloric canal; a second Fogarty balloon, passed down the second biopsy channel, records terminal antral contractions.

Eleven consenting patients who were found at routine endoscopy (under diazepam alone) to be free of structural gastroduodenal disease were studied for 10 minutes in the fasting state. In 85% of 92 isolated (unlinked) duodenal contractions the pylorus closed in response to the duodenal contraction. The pylorus probably prevents reflux by closing when an isolated duodenal cap contraction occurs.

F33 Demonstration of HCO₃⁻ secretion by the human stomach in vivo

W D W REES, G WARHURST AND L A TURNBERG (University Department of Medicine, Hope Hospital, Salford) Alkali secretion by gastric epithelium may be an important protective mechanism against damage by acid. We quantified gastric HCO₃⁻ production and duodenogastric reflux of HCO₃⁻ in the intact human stomach.

In 12 healthy fasting subjects the stomach was perfused with 3H₂O polyethylene-glycol, the duodenum with ¹⁴C polyethylene-glycol, and samples were aspirated from the antrum and jejunum. Acid secretion was suppressed by cimetidine (200 mg three hourly intravenously).

Total gastric and refluxed HCO₃⁻ was calculated from pH, PCO₂, and marker concentrations in fresh 10-minute aspirates for six hours. Validation studies showed good correlation between instilled and calculated, recovered gastric HCO₃⁻ (r=0·97, p<0·001, n=6).

Gastric HCO₃⁻ output in 12 subjects was 361±160 μmol/hour (range of mean hourly outputs 325–392). Duodenogastric HCO₃⁻ reflux was 40±18 μmol/hour (range of means: 23–63). The effect of topical prostaglandin E₂ (10⁻⁸ and 10⁻⁷M), an agent known to enhance mucusal resistance, on HCO₃⁻ output was examined (n=6). Luminal concentrations of E₂ were increased from 2·15±0·42 (basal) to 3·43±0·79 (10⁻⁷M) and 9·95±1·30 (10⁻⁸M) ng/ml respectively, but gastric HCO₃⁻ production remained unaltered. Duodenogastric reflux of HCO₃⁻ increased, however (p<0·05, n=6).

We have developed a method for simultaneous measurement of gastric and refluxed HCO₃⁻ in the human stomach. Basal HCO₃⁻ production is equivalent to 10% of basal acid secretion and was not altered by topical prostaglandin E₂.

F34 Secretin stimulation of high viscosity mucus glycoprotein aggregates in gastric juice

R KAURA, A ALLEN, AND B H HIRST (Department of Physiological Sciences, Medical School, University, Newcastle upon Tyne) Mucus in gastric juice can arise from either degradation by pepsin and mechanical erosion of the surface gel, or secretion. We have investigated these alternatives by characterising the mucus glycoprotein in gastric juice following secretagogues. Gastric secretions were analysed from six conscious, gastric fistula cats infused with secretin plus gastric volume stimulants: insulin, histamine, or pentagastrin.

Secretin (1 μg/kg/h) resulted in up to a tenfold increase in the reduced specific viscosity of gastric juice. Gel chromatography of the gastric juice showed the glycoprotein was not pepsin degraded whether secretin was infused or not. Centrifugation studies showed that the high viscosity during secretin was due to the presence of an aggregate, dependent on physical, non-covalent association of undegraded glycoprotein molecules. The amount of glycoprotein aggregate was reduced by raising the pH of the gastric juice to 7·0 or incubation at 37°C, which promoted endogenous peptic activity. These two procedures were associated with a fall in viscosity of over 60%.

These data are consistent with the stimulation of a newly secreted mucus glycoprotein by secretin. The high viscosity glycoprotein aggregate was a feature only of secretion infusions, and was not observed with the gastric volume stimulants alone.

F35 Study of the role of opiates in regulating motor and secretory function of the human upper gastrointestinal tract

W D W REES AND L A TURNBERG (University Department of Medicine, Hope Hospital, Salford) Endogenous opiates may modulate secretory and motor activity in the gastrointestinal tract. We studied the effect of an opiate antagonist, naloxone, and agonist, loperamide, on gastroduodenal and jejunal motility, acid secretion, duodenogastric reflux, and duodenal volume flow in six fasting subjects.
Gastric and duodenal volumes were measured by a double non-absorbable marker perfusion technique. Fifteen minute samples were aspirated from antrum and jejunum. Motor activity was simultaneously recorded from antrum, duodenum and jejunum using slowly perfused tubes. Naloxone (40 μg/kg/h) was administered on one day and placebo (saline) on another. The effect of intragastric loperamide (4 mg bolus in 2 ml) and placebo were assessed for 3-5 hours each on each day. Gastric samples were titrated (pH 7.0) and acid output calculated.

Naloxone abolished interdigestive motor activity in two subjects and reduced mean cycle duration (136 ±17 to 86 ±21 minutes, p < 0.025) and mean motility index per cycle in the others (antrum, 1083 ±145 to 412 ±119 mm²; duodenum, 1063 ±176 to 499 ±140 mm²; jejunum, 2030 ±824 to 1242 ±396 mm²; p < 0.05). These effects were reversed by intragastric loperamide. The length and propagation velocity of the activity front, basal acid secretion, duodenogastric reflux, and duodenal volume flow were unaffected by naloxone or loperamide.

These results suggest that endogenous opiates influence interdigestive motor but not basal secretory activity in the human upper gastrointestinal tract.

F36 Study of the factors involved in the mechanisms of gastric mucosal damage in the rat

M E Parsons, G Pipkin, and C A Price (introduced by W L Burland) (Smith Kline and French Laboratories, Welwyn) We have investigated gastric mucosal damage with sodium taurocholate (NaT) and aspirin in the rat using an ex vivo gastric chamber technique. It has previously been shown that, after ischaemia in this preparation, gastric mucosal haemorrhage occurs with an increase in fluid production and protein loss by the gastric mucosa; however, no change in H⁺ back diffusion was seen. Thus we can directly compare the factors involved in the effects of several agents which have been reported to damage the gastric mucosa in the same animal model.

Topical NaT (20 mM + 10 mM HCl) significantly increased H⁺ back diffusion from 9 ±0.3 to 19 ±2.3 μequiv/30 min (p < 0.05, n = 6), and Na⁺ gain from 50.0 ±8.8 to 99.0 ±6.3 μequiv/30 min (n = 6, p < 0.01). NaT did not cause gastric lesions under these conditions. Aspirin (80 mg/kg/h intravenously) plus topical HCl/mannitol (100 mM) caused a significant increase in H⁺ back diffusion from 68 ±5.7 to 97 ±5.4 μequiv/30 min (n = 6, p < 0.01), and a small but significant increase in Na⁺ gain from 40.6 ±7.2 to 59 ±8.4 μequiv/30 min (n = 6, p < 0.05). Blood and protein loss from the mucosa also occurred, although less than seen after ischaemia, and lesions occurred over 29.1 ±1.6% of the secretory mucosa. (n = 6).

Therefore, when considering the effects of a potential ‘cytoprotective’ agent, a variety of underlying mechanisms of gastric mucosal damage must be considered. The effects of histamine antagonists will be discussed.

F37 Somatostatin-28 is less potent than somatostatin-14 as an inhibitor of gastric exocrine secretion

B H Hirst, J M Conlon, J Holland, B Shaw, D H Coy, A V Schally (Departments of Physiological Sciences and Clinical Biochemistry and Metabolic Medicine, University of Newcastle upon Tyne, and Veterans Administration Medical Center, New Orleans) We compared the gastric exocrine inhibitory activities of somatostatin-14 with somatostatin-28, an N-terminally extended form of somatostatin-14 that has been isolated from the intestine and hypothalamus. Both peptides were synthesised by solid-phase methods.

Gastric secretory studies were carried out in six conscious, gastric fistula cats. Gastric secretions were stimulated by pentagastrin, 8 μg/kg/h.

The exogenous doses of somatostatin-14 and somatostatin-28 required for 50% inhibition (ID₉₀) of pentagastrin-stimulated acid secretion were 1.65 ±0.17 and 4.83 ±0.51 nmol/kg/h, respectively. Both peptides were approximately five times more potent against pentagastrin-stimulated pepsin secretion; ID₉₀: somatostatin-14, 0.28 ±0.07 and somatostatin-28, 0.96 ±0.08 nmol/kg/h. Therefore somatostatin-28 is one-third as potent as somatostatin-14 when expressed in terms of exogenous doses. Circulating concentrations of somatostatin measured by radioimmunoassay are greater than five times higher during infusions of somatostatin-28 compared with somatostatin-14. Therefore these studies demonstrate that somatostatin-14 is at least 10 times more potent than somatostatin-28 when expressed in terms of circulating concentrations.

These data are consistent with somatostatin-28 being the precursor of the active peptide, somatostatin-14, involved in the control of gastric exocrine secretions, since prohormones are generally less potent than their product.

F38 H₂-receptor antagonists, carbenoxolone, and prostaglandin production in the stomach

A Martin, G C Sturniolo, and R Naccarato (Cattedra di Gastroenterologia, Clinica Medica I, Università di Padova) Some actions of H₂-receptor antagonists and carbenoxolone (CBNX) on the stomach are shared by prostaglandins (PG), but the relationship between these drugs and PG is still largely unknown. We tested whether cimetidine, ranitidine, and CBNX increase PG production in the rat stomach. Fragments of corpus and antrum were incubated for 120 minutes with either cimetidine 10 μg/ml or ranitidine 1 μg/ml or CBNX 2.5 mg/ml. Fresh medium was replaced every 30 minutes and the PG of the E group (PGE) released in the incubation mixture were assayed by RIA. Cimetidine and ranitidine did not affect PG production, while CBNX increased PGE liberation fourfold (controls =0.37; CBNX=1.66 ng PGE/100 mg tissue/30 min, p < 0.01). Since several PG are cytoprotective, we then studied in vivo whether treatment with CBNX could determine cytoprotection. In the rat, CBNX (1.4 mg/kg) given orally 30 minutes before oral administration of 1 ml absolute ethanol markedly reduced the number and severity of the gastric lesions. We conclude that, in the stomach, unlike H₂-receptor antagonists, CBNX significantly increases PG liberation by either stimulating their synthesis or inhibiting their catabolism; that CBNX has cytoprotective properties; and that these effects of CBNX may have important therapeutic implications.

F39 Regulatory peptides in the human fetal stomach

B A Stein, A M J Buchan, M G Bryant, M Gregor, J Morris, S R Bloom, J M Polak
(Histochemistry Unit, Departments of Histopathology and Medicine, Hammersmith Hospital, London, and Department of Human Anatomy, Oxford) The role of regulatory peptides in the development of the gastrointestinal tract is interesting in view of their proposed trophic effect (for example, gastrin and enteroglucagon). We previously demonstrated a distinct developmental pattern for a number of regulatory peptides in the intestine. We examined the stomach (fundus and antrum) of 25 fetuses aged 8–40 weeks by immunocytochemistry and radio-immunooassay for the presence of gastrin, somatostatin, and glucagon. Gastrin in the antrum and somatostatin in both regions were present from eight weeks onwards and glucagon (in the fundus) from 10 weeks. Gastrin and somatostatin cell numbers increased from eight weeks to term (for example, antral somatostatin 11±0.4 cells/mm, 24±5±6-2 cells/mm, 48±1±0.3 cells/mm, mean±SEM). Glucagon-immunoreactive cells increased significantly from 0.2±0.1 cells/mm at 12 weeks to 3±6±1.5 cells/mm at 14 weeks and remained stable to birth. Radioimmunoassay of tissue extracts showed a similar developmental pattern; for example, glucagon detectable at 8 weeks increased by 40 pmol/g wet weight by 14 weeks and remained at this level to term.

The development of these peptides paralleled that of the growth of the entire stomach. Glucagon reported in the fundus of several mammals has not previously been reported in human fundus. The fact that these peptides are present in young fetuses suggests a role in the maturation of the fetal gut.

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F40
Detection of HBV-DNA by molecular hybridisation: a more sensitive method for detection of HBV particles in serum

I V D Weller, M J F Fowler, J Monardino, S Hadziyanis, A Craux, and H C Thomas (Departments of Medicine and Physiology, Royal Free Hospital, and School of Medicine; Academic Department of Medicine, Hippokration General Hospital, Athens) Existing methods for measuring viral DNA in the serum of patients with chronic HBV infection are either insensitive or indirect. A modification of a method is described in which Dane particle associated DNA is extracted from a small volume of serum and detected by hybridisation using 32p-labelled cloned HBV DNA (donated by J Summers) or HBV DNA extracted from the serum of an immunosuppressed patient, followed by autoradiography and densitometry.

Serial estimations of serum HBV DNA in patients treated with antiviral therapy showed a positive correlation with HBV DNA polymerase but viral DNA was still detectable in low concentrations in the presence of anti-HBe. Furthermore, in some patients with anti-HBe and HBV DNA in the serum HBcAg was detected in the liver by immunofluorescence.

The method has been estimated to be 50–100 times more sensitive than the HBV DNA polymerase assay. The use of an assay with higher sensitivity has allowed for the detection of HBV DNA in patients with anti-HBe and provides an explanation for the transmission of infection that has been reported in some of these patients.

F41
Family screening in 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) Acute intermittent porphyria (AIP) is an autosomal dominantly inherited disorder of haem biosynthesis characterised by reduced activity of the enzyme uroporphyrinogen I synthase and compensatory increased activity of the rate controlling enzyme, delta-aminolevulinic acid (ALA) synthase. Subjects with the disorder should be identified as they are at risk of developing severe porphyrinic attacks if exposed to a variety of drugs or chemicals. We have assessed the value of measuring in peripheral blood cells the activities of ALA synthase and URO synthase as a means of identifying latent cases in affected families.

In AIP subjects, ALA synthase activity was increased and URO synthase decreased compared with controls, though there was considerable overlap between the two groups when either enzyme was examined alone. When both enzymes were examined together, all but one of the 19 AIP patients had both increased ALA synthase activity (>250 nmol ALA/g prot/h) and reduced URO synthase activity (<25:1 nmol URO/l RBC/h). None of the 62 controls showed this enzyme pattern. Examination of 35 asymptomatic first degree blood relatives of AIP patients showed that 17 (49%) had the porphyrinic enzyme pattern with no sex bias. The combined study of these two enzymes permits accurate detection of latent cases of AIP and confirms its autosomal dominant sex-independent inheritance.

F42
Platelet thromboxane production in alcoholic liver disease

I G Barrison, L Viola, and I M Murray-Lyon (Gastroenterological Unit, Charing Cross Hospital, London) Thrombocytopenia, impaired platelet aggregation, and reduced platelet survival are common findings in patients with alcoholic liver disease. In vitro studies in which platelets from normal volunteers were incubated with increasing concentrations of ethanol have shown that platelet thromboxane production (PTP) was impaired with alcohol concentrations greater than the equivalent of 200 mg/100 ml blood. The aim of this study was to establish whether PTP in patients with alcoholic liver disease was similarly impaired.

Twenty-two patients and 11 normal controls were studied (14 patients with alcoholic cirrhosis and eight with alcoholic hepatitis and/or steatosis). The diagnosis was made by liver biopsy in all cases. PTP was determined by Stuart’s method, in which platelets are aggregated by thrombin; one of the products of aggregation, malonaldehyde, is measured spectrophotometrically, and expressed as nmol malonaldehyde/10⁹ platelets (nm mol/10⁹ platelets). Control PTP was 1.01±0.09 nm mol/10⁹ platelets. Control PTP was 1.01±0.09 nm mol/10⁹ platelets (mean±SE); PTP in patients with alcoholic cirrhosis was 3.37±0.64 nm mol/10⁹ platelets; this was significantly greater than controls (Wilcoxon’s rank sum, p<0.05), and patients with alcoholic hepatitis/steatosis, where PTP was 1.07±0.21 nm mol/10⁹ platelets (p<0.05).

This study shows that PTP is enhanced rather than impaired in patients with alcoholic cirrhosis. It appears that once platelet aggregation has occurred in patients with alcoholic cirrhosis platelet thromboxane may be more readily available to initiate further aggregation.
Liver copper content of DL ethionine treated rats

M H JAMISON, M BELL, R M CASE, H WHITWELL, AND J M BRAGANZA (University Department of Gastroenterology and Biochemistry Department, Manchester Royal Infirmary, and Departments of Physiology and Pathology, University of Manchester) Both biliary copper secretion and serum copper oxidase activity are higher in untreated patients with chronic pancreatitis (without bile duct obstruction) than in controls. We have studied the effect of experimental pancreatic damage on hepatic copper content in chronic experiments in rats.

Three groups of rats (initial weight 100 g) were investigated: group 1, normal diet; group 2, normal diet with 0.5% DL ethionine; group 3, normal diet with 0.5% DL ethionine + pancreatic extracts (Pancrex V 7-6 g/kg). Animals were killed at 5 weeks. Liver copper was measured by atomic absorption spectrometry after dry ashing. Liver copper in group 1 was 21.0±1.98 μg/g dry weight. In group 2 liver copper was significantly raised (54.7±7.7 μg/g) (mean±SEM; n=5; P<0.02). In group 3 liver copper was significantly less than group 2 (29.3±1.6 μg/g) (mean±SEM; n=5; P<0.05) though it still remained significantly higher than group 1. DL ethionine caused selective atrophy of pancreatic exocrine tissue with minimal histological changes in the liver.

We conclude that pancreatic insufficiency caused by DL ethionine leads to an increase of liver copper. This copper accumulation is significantly reduced by feeding pancreatic extracts.

Zinc status in alcoholic cirrhosis

P R MILLS, G S FELL, R G BESSENT, L NELSON, AND R I RUSSELL (Gastroenterology Unit and Departments of Biochemistry and Nuclear Medicine, Royal Infirmary, and Department of Clinical Physics and Bioengineering, Glasgow) Alcoholic cirrhosis (AC) is often said to be accompanied by zinc deficiency because of the finding of low serum zinc concentrations, increased urinary excretion and clearance of zinc, and decreased hepatic zinc concentrations. An evaluation in males of hepatic zinc and alcohol dehydrogenase (ADH) concentrations and whole body zinc, using 65Zn, was undertaken in AC (13 patients) and the following controls: elective abdominal surgery (10) and healthy volunteers (13).

Hepatic zinc concentrations (mean±SD) were significantly lower in AC patients than controls (0.38±0.18 v 1.05±0.38 μg/mg protein, P<0.001). Hepatic ADH activity, a zinc metallo-enzyme, was also depressed in AC (1.92±1.4 v 5.2±2.4 units/g protein at pH 10.1, P<0.01) and showed a correlation with hepatic zinc concentrations (r=0.46, P<0.05). Seven-day retention of oral 65Zn (% absorption) was increased in AC (43.1±16 v 26.9±14%, P<0.05) and whole body zinc levels were also significantly higher in AC (1.69±0.55 v 0.89±0.45 g, P<0.005). This study has demonstrated that AC patients have increased intestinal absorption and whole body content of zinc, despite apparent hepatic zinc deficiency. Hepatic ADH activity was depressed and correlated with changes in hepatic zinc concentrations. Portosystemic venous shunting might divert ingested zinc away from the liver to accumulate in extrahepatic tissue stores.

Antibodies to the surface of alcohol-pretreated rabbit hepatocytes in patients with alcoholic liver disease

J NEUBERGER, A L W F EDDLESTON, M DAVIS, AND R WILLIAMS (Liver Unit, King's College Hospital, London) To investigate further the presence of immunological abnormalities in alcoholic hepatitis and cirrhosis sera from patients with alcoholic liver disease were tested for antibodies reacting with the plasma membrane of liver cells isolated from ethanol pretreated rabbits ('alcohol hepatocytes'). Sera were previously absorbed with control hepatocytes to remove auto-antibodies. With indirect immunofluorescence, a distinct granular pattern of membrane fluorescence was seen on 'alcohol hepatocytes' incubated with sera from nine of 15 patients with alcoholic hepatitis with or without cirrhosis.

The presence of this antibody was investigated further using an induced cytotoxicity assay, in which antibody-coated hepatocytes were rendered susceptible to lysis in vitro by normal lymphocytes. Sera from 25 of 45 patients with alcoholic hepatitis with or without cirrhosis induced significant cytotoxicity to 'alcohol' but not control hepatocytes, compared with only one of 14 patients with uncomplicated alcoholic fatty liver. The involvement of antibody in the cytotoxic reaction was confirmed by the loss of cytotoxic effect after absorption of sera with 'alcohol hepatocytes,' or addition to the assay system of the F(ab)2 fragment of antibody to the Fc portion of human immunoglobulin. Cytotoxicity to 'alcohol hepatocytes' was not induced by sera from normal controls or patients with acute or chronic viral, drug, or autoimmune liver disease.

These results provide the first evidence that alcoholic hepatitis in some patients is associated with sensitisation to ethanol-altered hepatocyte membrane components which could play a role in determining susceptibility to the disease and its progression.
healing and return of biochemical values to normal, and therefore does not support concepts of disturbed 25-hydroxylation of vitamin D or tissue resistance to 1-25 dihydroxyvitamin D3 in chronic liver disease.

F47
Controlled trial of injection sclerotherapy in patients with cirrhosis and variceal haemorrhage

B R D MACDOUGALL, D WESTABY, AND R WILLIAMS (Liver Unit, King’s College Hospital, London) In a prospective randomised controlled clinical trial involving 106 patients with cirrhosis and recent proved variceal bleeding, repeated injection sclerotherapy was compared with medical management alone for the prevention of recurrent haemorrhage from oesophageal varices. Injection sclerotherapy was carried out using a fiberoptic endoscope and flexible oesophageal sheath, and repeated at three-weekly intervals until oesophageal varices were obliterated at the gastro-oesophageal junction. Overall, 23 (46%) of the 50 patients in the sclerotherapy group had further bleeds compared with 42 (75%) of the 56 patients receiving standard medical treatment. Rebleeding in the sclerotherapy group was mainly during the first three months before obliteration of varices and thereafter the frequency of recurrent haemorrhage in this group was significantly reduced (32%; p < 0.01). The risk of bleeding per patient-month follow-up decreased threefold with sclerotherapy and this was irrespective of the degree of hepatic decompensation. Overall survival assessed by cumulative life-table analysis was significantly improved in the sclerotherapy group (p = 0.012) with only four deaths due to bleeding compared with 17 in the medical treatment group. These results show that, in patients with cirrhosis, repeated injection sclerotherapy significantly reduces recurrent bleeding from oesophageal varices and improves overall survival; and, of particular note, this is also achieved in poor risk patients.

Department of Medicine, St George’s Hospital Medical School, London) Cholesterol crystal dissolution in unsaturated bile is much faster than crystal growth in metastable supersaturated bile, so that the least saturated gall bladder sample of the day may be the most important in determining gall stone dissolution during bile acid treatment. A diurnal variation in cholesterol saturation index (SI) has been demonstrated for hepatic but not for gall bladder bile. We have therefore compared SI of gall bladder bile obtained by nasoduodenal intubation and cholecystokin infusion at 9 am after the conventional 12 hour fast, with that obtained at 5 pm, five hours after a meal containing no cholesterol or phospholipid.

In order to avoid measuring inorganic phosphate, all three biliary lipids were determined enzymatically. In healthy controls, SI (mean ± SEM) fell from 1.02 ± 0.08 at 9 am to 0.86 ± 0.08 at 5 pm (n = 8; p < 0.05); in cholesterol gall stone patients SI fell from 1.36 ± 0.07 to 1.04 ± 0.07 (n = 8; p < 0.05); on chenodeoxycholic acid 15 mg/kg/day SI fell from 0.91 ± 0.06 to 0.78 ± 0.07 (n = 16; p < 0.01). The afternoon SI was > 1.02 in 4/4 patients whose stones did not dissolve and in 0/12 whose stones did dissolve. The morning SI was > 1.02 in three patients from both groups. We conclude that it is feasible to measure SI postprandially; that there is a diurnal variation in SI of gall bladder bile; and that postprandial SI may be more relevant than fasting SI in studying gall stone dissolution.

F48
Diurnal variation in cholesterol saturation of gallbladder bile

R M KUFFER, R P JAZWARI, AND T C NORTHFIELD (Norman Tanner Gastroenterology Unit, St James’s Hospital, and

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refined sugar (mean ± SEM: 106 ± 7 vs 6 ± 1 g, p < 0.001), less dietary fibre (13 ± 1 vs 27 ± 3 g, p < 0.001), and more energy (2192 ± 157 vs 1712 ± 153 kcal, p < 0.001). Average weight rose 1.6 kg on this diet and fell 1.5 kg on the unrefined diet. Protein, fat, and cholesterol intakes were not significantly different.

Bile cholesterol saturation index was higher on the refined diet (1.50 ± 0.10 vs 1.20 ± 0.12, p < 0.005). Analysis of individual bile acid composition showed less cholic acid (36.4 ± 1.9 vs 42.1 ± 1.9%, p < 0.002) and more deoxycholic acid (28.7 ± 2.8 vs 25.1 ± 2.4%, p < 0.02) on the refined diet. Chenodeoxycholic acid and lithocholic acid were unchanged. There were no significant differences in bile acid pools measured by isotope dilution in seven subjects on refined vs unrefined diets (total 4.98 ± 0.57 vs 4.67 ± 0.33 mmol; cholic acid 1.97 ± 0.23 vs 2.18 ± 0.11; chenodeoxycholic acid 1.18 ± 0.15 vs 1.04 ± 0.12), nor in primary bile acid synthesis or fractional turnover rates.

Consumption of carbohydrate in refined form increases bile cholesterol saturation. This effect is probably due to alterations in bile acid pool size.

F50
Rapid small intestinal transit in gallstone patients

R M KUFFER, M GANNON, AND T C NORTHFIELD (Norman Tanner Gastroenterology Unit, St James’s Hospital Medical School, London) Bile acid pool size is reduced in gall stone patients but is inversely related to recycling frequency. Increased recycling frequency of the bile acid pool may be due to rapid small intestinal transit. We have therefore measured small intestinal transit time in 25 subjects with radiolucent gall stones in a radiologically functioning gall bladder and in 15 normal controls. We used a modified hydrogen test which employs a sensitive semiconductor system, allowing use of a solid test meal as a more physiological stimulus than the conventional lactulose. The technique was reproducible; duplicate studies on six patients gave coefficient of variation of 8%. Small intestinal transit time (mean ± SEM) was 174 ± 10 min in gall stone patients and 223 ± 17 min in control subjects (p < 0.01 by unpaired Wilcoxon test). Seven gall stone patients were restudied during treatment with chenodeoxycholic acid 15 mg/kg/day. Mean transit time before treatment was
F51
Bilirubin-cholesterol saturation index (BrCSI): a new index to predict lithogenicity in cholesterol gall stone (CGS) disease

M K Dutt, Barbara Murray, R Jazrawi, R Kuper, T C Northfield, and R P H Thompson (Gastrointestinal Research Unit, St Thomas’s Hospital, London, and Department of Medicine, St George’s Hospital, London) The cholesterol saturation index (CSI) has greatly increased understanding of CGS formation but controls often have raised CSI. CSI > 300% (rarely found) is necessary to predict stone formation, assuming homogeneous (spontaneous) cholesterol precipitation. Stones usually have pigmented centres, so heterogeneous nucleation and growth is likely. We believe highly insoluble unconjugated bilirubin (uBr) is crucial to CGS formation. Therefore BrCSI was devised from detailed uBr equilibrium solubility limits in model bile, using a new co-precipitation technique. The end point is biliary saturation with uBr, but important interactions of uBr and cholesterol were allowed for, together with varying bile acid, lecithin and total lipid concentrations.

Bile (29 CGS patients, 13 normal subjects) was analysed for lipids and absolute uBr amounts measured by improving a previous TLC method. Median BrCSI was 110 in patients, 50 in normal subjects; conventional CSI (Carey and Small 1978) 112 and 92 respectively. BrCSI was more specific than CSI; BrCSI > 100% in 1/13 normal subjects, 18/29 patients; CSI > 100% in 6/13 normal subjects, 23/29 patients; Youden's index (1-combined error probabilities) strongly favoured BrCSI (0.544); cf CSI (0.331). Furthermore, BrCSI > 100% derived from heterogeneous phase systems directly predicted uBr precipitation, whereas CSI 100-300%, derived from homogeneous systems, only indicates metastable cholesterol, which requires additional nucleation factors—for example, uBr—to precipitate and form stones. This new index should prove of theoretical and practical interest.

F52
Bile acid feeding and cholesterol absorption: the effect of deoxycholic (DCA) and cholic (CA) acid pool expansion

M Ponz de Leon, N Carulli, P Loria, R Iori, and M Romani (Istituto di Clinica Medica II, Università di Modena and Divisione di Chirurgia Castelfranco Emilia, Modena) It has been suggested that chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA) feeding decreases dietary cholesterol absorption and that this effect could contribute to bile desaturation. To further investigate the mechanisms of bile acid induced changes of cholesterol absorption we studied the effect of DCA and CA feeding on cholesterol absorption and bile saturation. Eighteen volunteers were treated for three weeks with either DCA (n 9, 15 mg/kg/day) or CA (n 9, 15 mg/kg/day) plus oral ampicillin (2-4 g/day) to suppress part of the intestinal bacteria responsible for CA desaturation and therefore to selectively expand the CA pool. Dietary cholesterol absorption, bile lipid composition, and bile acid pool size were measured in each patient both before and after treatment.

The administration of either bile acids resulted in a significant increase of the respective pool size. After DCA feeding, cholesterol absorption was significantly reduced (21.0±5.1% of the given dose versus 38.7±12.6%, mean ±SD, P<0.01), whereas the absorption values were sharply increased following CA pool expansion (48.3±11.1% versus 31.4±6.5%, P<0.01). Bile saturation significantly increased (P<0.02) after DCA, but tended to fall after CA feeding. In conclusion, our data suggest that CA probably plays a key role in promoting cholesterol absorption in humans. Similarly to CDCA and UDCA, DCA feeding induces cholesterol malabsorption, possibly owing to the reduction of CA pool size. Finally, changes of cholesterol absorption do not seem to bear any relation to bile saturation.

F53
Evaluation of flexible sigmoidoscopy in a surgical rectal clinic

R J Nichols, R J Leicester, and P R Hawley (St Mark’s Hospital, London) Flexible sigmoidoscopy has been reported to increase the diagnostic yield of left-sided colonic lesions, but there is little information on its use in the UK. We have assessed the practicability of flexible sigmoidoscopy in surgical clinics and compared the diagnostic yield with rigid examination in 317 new outpatients.

Patients were selected by any of the following criteria: age >40 years, symptoms suggesting colorectal disease, past history of neoplasia, family history of colorectal cancer. Rigid sigmoidoscopy, followed by flexible sigmoidoscopy without sedation, after preparation with two phosphate enemas (200 ml), was performed by surgeons of varying endoscopic experience. Bowel preparation was good or adequate (some faecal contamination) in 254 (80%) and poor (faeces impairing or preventing examination) in 63 (20%). The mean distance of insertion was 48.9±12.7 cm for flexible and 17.7±4.3 cm for rigid examination. The sigmoid colon was reached in 310 (98%) of flexible sigmoidoscopies and the sigmoid-descending junction and splenic flexure estimated to be passed in 253 (80%) and 123 (39%) of cases. Abnormailties were seen on 121 (37%) flexible and 51 (15%) rigid examinations, with a fourfold increase in the detection of adenomas and carcinomas.

Outpatient flexible sigmoidoscopy proved feasible and was acceptable to the patient. It is valuable in detecting neoplasms, avoiding the delay in diagnosis before barium enema examination.

F54
Influence of size and design of endoscopic biopsy forceps on specimen weight and adequacy

B Danesh, M Burke, J Newman, P B Cotton (Gastrointestinal Unit and Bland Sutton Institute of Pathology, Middlesex Hospital and Medical School, London) We have compared the weight, depth, and
diagnostic adequacy of gastric biopsy specimens taken with 16 commercially available biopsy forceps of different size, shape, and make. Four hundred and seventy-six gastric biopsies were obtained at different pressures using an in vitro experimental design on human resected stomachs, and 60 specimens were obtained in vivo in the dog stomach. Greater pressure consistently provided significantly heavier, deeper, and more acceptable specimens. Standard-sized forceps (diameter 2-4 mm) produced significantly heavier specimens of better histological yield than those using paediatric forceps (diameter 1-8 mm) in vitro and in vivo. Ellipsoid cups produced larger specimens than round cups, but the histological yield was comparable. In vitro, fenestrated cups produced shallower and more fragmented specimens than those taken with normal cups. A spike in the forceps and their make had no influence on biopsy weight or adequacy. We are studying the clinical significance of these findings.

Eleven hundred samples were collected from endoscopes during routine gastrointestinal endoscopy procedures over a 12 month period; samples being taken from various sites of the gastro-intestinal tract using an endoscope immediately after endoscopy before cleaning and after disinfection with the agent. The results showed that after cleaning and disinfecting procedure lasting four minutes viable bacteria were found to be present in 12 of the 490 samples (3%). In view of this finding the cleaning procedure was extended to a total of six minutes, after which time no viable bacteria were recovered in the subsequent 700 samples.

P776 (Dettox) has proved to be an effective disinfectant and cleansing agent for between-patient endoscope preparation. It is non-irritant and therefore is acceptable to staff, and it produces no adverse effect on the instrument.
been no retained stones at follow-up to date.

We conclude that transduodenal exploration of the common duct, operative cholangiography, and a dependent drainage procedure should reduce or eliminate the problem of retained common duct stones.

F59
Clinical and endoscopic follow-up after duodenoscopic sphincterotomy

A G VALLON, P B COTTON, J HOLTON (Gastrointestinal Unit and Department of Microbiology, Middlesex Hospital and Medical School, London) Between 1975 and 1979, 163 post-cholecystectomy patients with common duct stones were successfully managed by duodenoscopic sphincterotomy. Follow-up information is available on 148 of them, at between one and six years (mean 31 months). Only six patients (4%) have had significant symptoms attributable to the biliary tract subsequently. Two had stenosed sphincterotomies and recurrent stones; four others with attacks of cholangitis had patent sphincterotomies (orifice > 5 mm). Only one had stones which had developed throughout the liver. Check ERCP in 23 other asymptomatic subjects showed a patent sphincterotomy and a normal biliary system. Bile was aspirated in 27 of the 29 patients undergoing ERCP; 17 (62%) had significant bacterial contamination (counts > 10^5/ml), in 13 cases with a single intestinal organism. Bacterial contamination was found most often in elderly patients with dilated ducts, but did not appear to correlate with the size of the biliary orifice; its clinical significance is uncertain, since most subjects are asymptomatic.

F60
Clinical trial of single or triple dilatation for benign oesophageal stricture

I F TROTMAN AND J J MISIEWICZ (Department of Gastroenterology, Central Middlesex Hospital, London) Dysphagia due to oesophageal stricture may be relieved by dilatation, but the best regime of management has not been studied prospectively. Nineteen patients with dysphagia and histologically benign oesophageal strictures were randomly allocated to receive either single dilatation (11), or three serial dilatations at fortnightly intervals (eight).

All dilatations were performed using the Eder-Puestow technique and the strictures diluted to 50 FG.

The two groups were well matched with respect to age, duration of dysphagia, number of previous dilatations, and interval since the last dilatation. Their ability to swallow was scored on a scale of 0-4 at monthly intervals after completion of the dilatation regime. Further dilatations were then carried out when there was a two or more point worsening of the clinical score, using the same protocol of single or triple dilatation in each patient. The results over a mean follow-up period of 20 weeks showed that patients allocated to the regime of triple dilatation had a significantly (p < 0.05) longer period of remission from dysphasia than did those undergoing single dilatation.

Triple dilatation of benign oesophageal strictures affords more sustained relief of dysphagia than single dilatation.

F61
Pneumatic dilatation for oesophageal achalasia

G F WATTS AND JOHN R BENNETT (Gastrointestinal Unit, Hull Royal Infirmary, Hull) Between 1970 and 1980 38 pneumatic dilatations were performed in 32 patients with radiologically and manometrically proved achalasia of the oesophagus. Thirty-three were performed by the Hurst-Tucker method, four using a Rider-Moeller dilator and one with a Pilling dilator. Thirty patients had a first dilatation, two having had both a previous dilatation and a Heller's cardiotomy. There were three recognised perforations (7.9%), two occurred with the Rider-Moeller, and one of the patients died.

Results were evaluated on strict clinical criteria with a median follow-up time of 3-67 years (0-58-9-50 years). Of the 37 analysed dilatations four (11%) were excellent, 16 (43%) were good, six (16%) were moderate, and 11 (30%) were poor. Of 30 first dilatations four (13.3%) were excellent, 12 (40%) were good, four (13.3%) were moderate, and 10 (33.3%) were poor. In Hurst-Tucker dilatations four (12%) were excellent, 14 (43%) were good, five (15%) were moderate, and 10 (33.3%) were poor. Of 10 patients with poor results six were redilated and three required a Roux-en-Y diversion for severe gastro-oesophageal reflux of which, one needed a previous dilatation of a peptic stricture. Another patient developed severe gastro-oesophageal reflux and a peptic stricture, but was not treated. Subjective results were better, 24 (65%) describing themselves as a lot better, seven (19%) as better, one (3%) as the same, five (12%) as worse, and none as a lot worse.

The objective symptomatic results are poorer than other published results of forceful dilatation.

GENERAL III
F62
Insights into the pathophysiology of the postvagotomy diarrhoea syndrome

S LADAS, P E T ISAACS, Y QUFESH, G MURPHY, AND G SLADEN (Gastroenterology Unit, Department of Medicine, Guy's Hospital and Medical School, London) Vagotomy and pyloroplasty is sometimes associated with incapacitating diarrhoea. The pathophysiology of this syndrome is unknown and an effective treatment has yet to be established. To investigate the role of the small intestine in this syndrome we studied intraluminal events after a liquid meal in normal subjects (N; n = 5), patients with postvagotomy diarrhoea (VP+D; n = 3), and patients without diarrhoea after vagotomy (VP−D; n = 2).

The volunteers swallowed a triple lumen tube and after an overnight fast were subjected to ileal perfusion (14C-PEG-saline) and given a liquid meal (300 ml, 460 mosmol/l, phenol red marker). Two fasting and eight postprandial 30 minute samples were collected from the jejunum and ileum. After the meal volumes entering the jejunum, estimated from phenol red dilution, were: N: 609 ± 184 ml (X ± SD), VP−D: 510, 600 ml, VP+D: 507, 536, 1095 ml. In all subjects jejunal osmolality increased postprandially to 360-400 mosmol/l and returned to isotonicity within three hours (normal subjects, two hours (VP−D), and 1½ hours (VP+D). Small bowel phenol red transit time was: N: 90-120 (range), VP−D: 45, 80, VP+D: 15, 17, 25 minutes. 2½ hours postprandial colonic inflow, calculated from 14C-PEG dilution, was N: 195 ± 25 (X ± SD), VP−D: 175, 181, VP+D: 781, 897, 985 ml. The calculated
osmotic load delivered to the colon because of nutrient malabsorption was: N: 0, VP-D: 7, 13, VP+D: 33, 43, 82 mosmol.

The failure of the small intestine to cope with hyperosmotic loads is an important factor in the pathophysiology of the postvagotomy diarrhoea syndrome.

F63
Zinc status in Crohn’s disease and ulcerative colitis

G C STURNOLO, G MASTROPAOLO, A MARTIN, G GURRIERI, R NACCARATO (Cattedra di Gastroenterologia, Università di Padova) Alterations of zinc status have been suggested in IBD and may have therapeutic implications. Aims of this study were to assess Zn status and to investigate the possible causes for Zn deficiency in patients with IBD.

In 46 patients with ulcerative colitis and 32 with Crohn’s disease we studied: Zn levels in plasma, urine, hair, and nails by atomic absorption spectrophotometry; Zn intestinal absorption by means of an oral Zn tolerance test; and taste and smell acuities, which are known to be altered in Zn deficiency.

Plasma Zn levels (in mg/100 ml) were significantly lower than normal in ulcerative colitis (99.8±22.3 SD) and Crohn’s disease (86.9±22.3) (normal 122.1±19.5), and were not correlated with the activity of the disease or with indices of malnutrition. Taste and smell functions were also significantly altered. Zn intestinal absorption was greatly impaired in ulcerative colitis (p<0.01) and Crohn’s disease (p<0.01). Urinary Zn excretion and hair and nail Zn levels were within the normal range in most patients. Conclusions: Zn status is altered in both ulcerative colitis and Crohn’s disease (low plasma levels, impaired taste and smell functions, reduced intestinal absorption). Reduced absorption, rather than increased urinary excretion, seems to be the key mechanism involved.

F64
Oral mannitol bowel preparations: a possible cause of postoperative sepsis

M R B KEIGHLEY, M M HARES, S BENTLEY, D YOUNGS, AND D W BURDON (Departments of Surgery and Microbiology, General Hospital, Birmingham) In a prospective study of sepsis after colorectal surgery 40 patients received oral mannitol bowel preparation and 32 were prepared by other methods, principally whole bowel irrigation. All patients received systemic antibiotic prophylaxis with either cefoxitin (C) or metronidazole and gentamicin (M + G).

There was no difference in the overall incidence of sepsis in patients who received cefoxitin (24%) compared with M + G (26%). The principal cause of sepsis was from Escherichia coli in both groups (22% of bacterial isolates). Mannitol was the only factor which could be implicated as a cause of sepsis in this trial, the rate of infection being 41% after mannitol compared with 16% after whole bowel irrigation (p<0.05). Mannitol was found to be associated with combustible gas in the colon. Bacterial counts of gas-producing Escherichia coli increased from 10^3 organisms/ml after whole bowel irrigation to 10^6 organisms/ml after mannitol.

A high sepsis rate occurred despite the use of antibiotics in patients receiving mannitol which was associated with a 10,000-fold increase in the counts of Escherichia coli. These data indicate that mannitol encourages overgrowth of gas-producing Escherichia coli in the colon which might be responsible for postoperative sepsis.

F65
Dynamic assessment of the faecal continence mechanism in man

W G HAYNES, M G READ, AND N W READ (Departments of Surgery and Physiology, University of Sheffield) The operation of the faecal continence mechanism was investigated in 18 normal subjects and 20 incontinent patients by carrying out anorectal manometry and electromyography during rectal infusion of 1 litre of saline. All subjects exhibited regular fluctuations in anorectal pressure and EMG occurring at a frequency of 1–3 per minute. In normal subjects these consisted of simultaneous rectal contractions, internal anal sphincter relaxations, and external sphincter contractions. Examination of the records suggested that continence in normal subjects is maintained by the tonic activity of the internal sphincter and its rapid recovery after relaxation with phasic contraction of the external sphincter playing an insignificant role.

In 13 incontinent patients, the ano- rectum behaved as one fluid-filled compartment. Regular contractions of the external sphincter were recorded on all channels; there was no evidence of IAS relaxations, and anal pressures were abnormally low. These observations suggest: the major defect in this group was a weak and easily inhibited internal sphincter tone; contraction of the external sphincter alone was unable to prevent incontinence. The remaining seven patients exhibited a normal pattern of pressure fluctuations, but had abnormally strong rectal contractions which exceeded the abnormally weak pressures in the anal canal.

F66
Is there a pelvic floor disorder in slow transit constipation?

D M PRESTON AND J E LENNARD-JONES (St Mark’s Hospital, London) Among patients complaining of constipation a group can be defined with slow whole gut transit but without megacolon or megarectum. It is not known whether their symptom is due to an abnormality of colonic motility or to a failure of the defaecatory mechanism.

To simulate defaecation experimentally the ability of such patients to expel from the rectum a balloon containing 50 ml of water has been studied. All 15 control subjects were able to expel the balloon unaidsed. None of the 15 constipated patients was able to expel the balloon and there was a resistance to expulsion in that the tension needed to pull the balloon out of the rectum while the patient strained ranged from 350 to 1150 g. When relaxed the tension needed to withdraw the balloon was not significantly different in normal subjects and in patients with constipation.

On electromyography of the pelvic floor muscles during attempts at expulsion of the balloon the normal inhibition of resting activity did not occur in any of the patients with constipation. Failure of sphincter relaxation on attempted defaecation appears to be a factor in ‘slow transit’ constipation.
F67
Acute necrotising colitis and colonic obstruction

C Teasdale and N J MCC Mortensen (Department of Surgery, Bristol Royal Infirmary) Acute necrotising colitis (NC) is a grave but rare complication of sigmoid colon obstruction. During a 20-month period we have seen six patients with NC proximal to an obstructing sigmoid carcinoma (five) or diverticulitis (one), suggesting that NC may be more common than previously recognised.

Altered bowel habit or abdominal pain was present for over six months in four patients. All six had rapidly deteriorated over six to 24 hours and were profoundly ill with hypertension, and a leucocytosis (mean 16x8). At laparotomy the entire proximal colon was affected, changes ranging from black mucosa to frank gangrene without perforation or major vessel occlusion. In one case this process extended into the terminal ileum. Four patients recovered after subtotal colectomy, but both patients with mucosal changes only who had a defunctioning colostomy died despite intravenous antibiotics. Histological changes in NC varied from mucosal necrosis to full-thickness gangrene. Gram stains of colonic wall demonstrated invasion with Gram positive rods identical to clostridia (five cases) or Gram positive cocci (one case). Cultures grew mixed bowel flora.

Early diagnosis and prompt treatment of partially obstructing colonic lesions will prevent this serious complication, and subtotal colectomy for established NC is mandatory.

F68
Does pentagastrin act by causing histamine release?

C J H Ingoldby, W K Man, and J Spencer (Department of Surgery, Hammersmith Hospital, London) The pattern of gastric histamine and acid secretion after pentagastrin infusion suggests that pentagastrin acts indirectly on the parietal cell by causing mucosal histamine release. If this is so, cimetidine blockade should inhibit pentagastrin-induced acid release, but not mucosal histamine secretion.

We have examined the effect of cimetidine on gastric acid, gastric histamine, and plasma histamine. Pentagastrin infusion (6 μg·kg⁻¹·h⁻¹) for two hours was performed on 13 subjects. Gastric acid secretion increased to median 50-4 mmol/h from basal levels, median 11-1 mmol/h. Gastric histamine output rose from median 3-9 nmol/h to 8-3 nmol/h in the 10-minute fraction (P<0-002). Plasma histamine rose from median 3-4 pmol/ml to 7-1 pmol/ml (P<0-01). Cimetidine 200 mg iv was given after one hour. Gastric acid secretion fell immediately to median 8-94 nmol/h (P<0-001). Gastric histamine output remained unchanged, median 7-38 nmol/h, although gastric secretion volume declined. Plasma histamine rose, median 11-6 pmol/ml, after injection (P<0-01). These results suggest that pentagastrin-induced gastric histamine secretion is not affected by an acid-inhibiting dose of cimetidine. The increase in plasma histamine suggests that parietal cell blockade leads to histamine spillover into the blood.

These data support the theory that pentagastrin acts indirectly on the parietal cell by inducing histamine release.

F69
Bombesin-stimulation test: a novel test for the assessment of the secretory antral function

J B M J Jansen, C B H W Lamers (Division of Gastroenterology, St Radboud Hospital, Nijmegen, Netherlands) At present no test for the secretory antral function is available. Postprandial gastrin release does not reflect the secretory antral function, because a meal releases gastrin from both antrum and duodenum. Antral biopsies have the disadvantage of sampling errors in patients with patchy gastritis. Bombesin is suggested to release gastrin selectively from the antrum. Therefore the serum gastrin response to bombesin might be a good measure of antral function.

We have compared antral histology and antral gastrin concentrations in patients with normal and with abnormally low integrated serum gastrin responses to bombesin (100 ng/kg, 20 min). Patients with abnormally low responses had integrated increases in serum gastrin in the same range (0-095-0-370 ng/ml 20 min) as found in 12 patients with antrrectomy (0-000-0-365 ng/ml, 20 min) Twelve subjects with normal responses to bombesin (0-565-9-375 ng/ml, 20 min) had significantly higher antral gastrin concentration (28±4.0 μg/g) than six patients with abnormally low responses (2-6±1.3 μg/g; P<0-001). Subjects with normal serum gastrin responses to bombesin had either normal antral histology or superficial gastritis, while antral histology in subjects with abnormally low responses ranged from superficial gastritis to atrophic gastritis. Four patients with low responses had achlorhydria and two normal acid secretion.

The serum gastrin response to bombesin is abnormally low in patients with low antral gastrin concentrations due to antral gastritis.

F70
Gastric juice nitrite and dysplasia after partial gastrectomy

N J MCC Mortensen, A Savage, S M Jones, M J Hill, and R J Marshall (Departments of Surgery and Pathology, Southmead Hospital, Bristol, and Bacterial Metabolism Research Laboratory, Colindale, London) Carcinoma developing in the gastric stump is a well-recognized late complication of gastric resection for benign disease, and dysplasia in gastric remnant mucosa may be premalignant. Gastric juice nitrite resulting from bacterial overgrowth in the hypochlorhydric stomach could be carcinogenic. In an endoscopic survey of 65 patients undergoing partial gastrectomy an average of 20 years previously biopsies were graded for mild, moderate, or severe dysplasia, and 12 patients with moderate dysplasia agreed to biannual review (follow-up 3-5 years). Gastric juice, pH, nitrites, and bacterial counts were measured.

In dysplasia patients average gastric juice pH was 7.3. Nitrite levels were raised in dysplasia patients: 36±8±4.5 (mean±SEM) μmol/l compared with controls: 17±0.5 μmol/l. There was a correlation (P<0.001) between pH and nitrite levels in the 65 patients. Bacterial counts >10⁹ organisms/ml were found in seven of 10 with dysplasia, and in five of these there were three or more species. Oral rather than intestinal flora predominated, and all species of staph and strep reduced nitrate to nitrite.

The presence of nitrate-reducing organisms in the gastric juice of dysplasia patients together with raised nitrite levels may be implicated in the induction of dysplastic changes in the gastric stump.
F71
Human pancreatic adenocarcinomata (HPA) in nude mice (NM) and artificial capillary culture (ACC)

M D TURNER, S KAJIJI, P A MEITNER, D DEXTER, N LAPOSTA-FRAZIER, H A BOGAARS, AND P CALABRESI (Roger Williams Hospital/Brown University Cancer Centre, and VA Medical Center, Providence, RI) COLO 357' a cell line from HPA established by Dr George Moore, was received as a monolayer and had not been grown previously in perfused ACC or NM. It was first grown as a monolayer; doubling time, cloning efficiency, saturation density, and response to a variety of chemotherapeutic agents were determined. COLO 357 was grown to a solid mass in ACC in 49 days. Glucose consumption increased exponentially for 42 days, and several tumour products were identified in the culture fluid. 10⁶ cells of COLO 357 injected subcutaneously into each of two NM gave enlarging nodules after one week. After four weeks the nodules were removed and shown to be typical mucosaproducing adenocarcinoma. One millimetre cubes of these were implanted subcutaneously into five more mice.

Palpable tumours appeared one week later; dimensions were measured every five days and tumour mass estimated from: mass (mg) = W³/4 (mm). After 30 days' growth the average estimated tumour weight in the five mice was 72 mg. After 38 days little further growth was apparent. Tumours were resected on day 46; their final weight averaged 102 mg. Two new HPA (RWP 1 and RWP 2), obtained at surgery, were inoculated into nude mice to produce visible tumours. To date RWP 1 has been passaged as one millimetre cubes in NM in a manner similar to that used for COLO 357. RWP 1 grew initially more rapidly than COLO 357 and continued to show exponential growth until it was resected at 46 days. Two mice survived resection of the primary tumour for six weeks and showed pulmonary metastases at necropsy.

We have now established four HPA in NM, one of which metastasises, and three in capillary cultures. They can be used for metabolic studies and investigation of therapeutic modalities.

F72
In-vitro studies of cell birth rates in human colorectal tumours compared with normal mucosa

C J PRITCHETT, P V SENIOR, J P SUNTER, A J WATSON, D R APPLETON, AND R G WILSON (Departments of Surgery, Pathology and Medical Statistics, University of Newcastle upon Tyne) It is well known from clinical observation that an unrected rectal carcinoma may take several years to grow large enough to cause symptoms. What little kinetic data exists from in vivo studies suggests that tumour cells cycle more slowly than mucosal cells.

We have used a short-term organ culture technique to provide numerous tissue explants from surgical excision specimens in order to overcome the enormous limitations and inherent inaccuracies of in vivo studies. In our system, tissue appeared to recover from the trauma of explantation by 18 hours and thereafter statomokinetic studies were carried out using vincristine to arrest mitosis and provide cell birth rates from rates of metaphase accumulation.

Two controlled dose response experiments demonstrated a sixfold difference between mucosa and tumour in the minimum dose of vincristine required for complete metaphase arrest, tumour being more resistant. This may partly explain the resistance in clinical practice to such cytotoxic drugs.

Using vincristine concentrations of 0.5 mg/l for mucosa and 3.0 mg/l for tumour, eight further experiments were carried out. The mean of the cell birth rates in mucosa was 7.73 cells/1000 cells/h and in tumour 10.21 cells/1000 cells/h, a significantly faster rate (P=0.009). This is at variance with previous observations in the literature.

F73
Experimental colon carcinogenesis is facilitated by endogenous factors in the intestinal contents

G P FERULANO, J P CRUSE, M R LEWIS, AND C G CLARK (Surgical Unit, School of Medicine, University College, London: Rayne Institute, London) The theory that endogenous factors in the intestinal contents may be pathogenic during large bowel carcinogenesis was tested in the dimethyldihydrazine (DMH)-induced rat colon cancer model.

Thirty female Wistar rats had a surgical transection of their proximal colon with reanastomosis to the rectum, thereby excluding part of the colon from faecal contact. All rats then received a course of DMH (40 mg/kg body wt/wk subcutaneously for 10 weeks) while fed on Vivo-nex. The diet was selected because it lacks any known exogenous (dietary) cocarcino gens. It also produces mucus atrophy in functioning (proximal) colon, to parallel the disuse atrophy induced in the defunctioned (distal) colon. Animals were reared on the diet throughout the experiment and were killed when moribund or at 40 weeks. At necropsy, the anatomical distribution, number, and histological type of colon tumours were compared between functioning and defunctioned colonic segments within the same animal. The results showed that there were both fewer tumours (P<0.01) and fewer carcinomas (P<0.02) in the defunctioned segment compared with the proximal colon. The fact that carcinoma may occur in the defunctioned segment indicates that colon cancer can develop in the absence of faecal contact.

The data indicate that endogenous factors in the intestinal contents facilitate chemically induced colon carcinogenesis.

F74
Effect of warfarin on colorectal cancer in the experimental model

B MOONEY AND I TAYLOR (Department of Surgery, University of Liverpool) A study of the effect of warfarin on the natural history of azoxymethane-induced colorectal cancer in the rat has been carried out. Fifty rats were treated with azoxymethane in a dose of 10 mg/kg/wk for 12 weeks. They were then divided into two groups. One group acted as a control while the other was treated with warfarin (0.2 mg/l) in their drinking water for six weeks. In so far as was possible coagulopathy was prevented. The animals were allowed to survive until signs of disseminated disease developed. Laparotomy and necropsy were then carried out.

The number of primary colorectal tumours in the warfarin treated group (155) was statistically significantly less than that in the control group 255 (P<0.05). It was demonstrated that the warfarin-treated group of animals was adequately anticoagulated (mean prothrombin time 24.3±8.4 s, standard deviation 10.6 s). The number of lung and liver metatases were also statistically significantly reduced in the warfarin-treated
group (four) compared with the control group (12) (p < 0.02).

This study suggests that not only does warfarin have antimitastatic properties but apparently inhibits primary tumour growth also. It may also be a beneficial adjuvant to surgery in the management of curable colorectal cancer.

F75
Dietary and endogenous sources of carbohydrate substrate in the human colon
A M STEPHEN, A C HADDAD, AND S F PHILLIPS (Gastroenterology Unit, Mayo Clinic, Rochester, USA) Dietary fibre is considered the major source of carbohydrate substrate for the colonic microflora. However, as determined indirectly using breath hydrogen production, dietary starch is absorbed incompletely from the small intestine even in health. We therefore estimated directly the unabsorbed fraction of dietary starch, using intubation techniques.

Healthy volunteers (n=7) had a multilumen tube positioned fluoroscopically for aspiration close to the ileocaecal junction. 14C-PEG was perfused above the aspiration site to estimate flow by marker-dilution. On consecutive days, subjects ate two liquidised meals containing 20-0 or 60-8 g starch and 15 g PEG. Ileal samples, collected each 15 minutes for five to six hours fasting and six to seven hours after meals, were analysed for starch (amyloglucosidase) and multiplied by flow/15 minutes to derive starch unabsorbed from the meal. Recovery of PEG was used to assess passage of meals. Fasting samples were analysed colorimetrically for hexosamine, to determine endogenous carbohydrate entering the colon as glycoproteins.

Unabsorbed starch varied from 455 to 4023 mg (2-3 to 20-1%) for the 20 g meal and 1332 to 6352 mg (2-2 to 10-4%) for the 60-8 g meal. Mean (±SEM) values were 1862±607 mg and 3640±732 mg respectively (9-3% and 6-0%). Recovery of hexosamine varied from 30-2 to 115-4 mg/h (mean 71-9±10-0 mg/h), corresponding to approximately 150 mg carbohydrate/h. We conclude that 5 to 10% of dietary starch escapes small bowel absorption and, with a smaller contribution from endogenous glycoproteins, provides considerable substrate for growth of colonic microflora.

F76
Pharmacological inhibition of chenodeoxycholate-induced fluid and mucus secretion and mucosal injury in rabbit colon
M CAMILLERI, R MURPHY, AND V S CHADWICK (Gastroenterology Unit, Department of Medicine, Royal Postgraduate Medical School, London) The effects of various pharmacological agents on chenodeoxycholate (CDC)-induced fluid secretion, mucus secretion (protein bound hexose output), and mucosal injury (DNA output) were investigated using a perfusion technique in the rabbit colon. Each agent was tested in five rabbits and statistical analysis was by Wilcoxon stratified test.

Atropine (1-6 μg/kg/min IA) reduced and carbachol (1 μg/kg/min) potentiated the fluid secretion (37% reduction and 135% increase respectively), mucus output (65% reduction and 72% increase respectively), and mucosal damage (65% reduction and 55% increase respectively) produced by 5 mM CDC. In contrast, pretreatment of the colonic mucosa with lignocaine (1% w/v) and parenteral administration of methysergide (11 μg/kg/min) and somatostatin (0-7 μg/kg/min) produced a reduction (50%, 39%, 29% respectively) in fluid secretory response without apparent effects on mucus output or mucosal damage. Topical pretreatment of the colonic loop with loperamide (0-8 mg/kg) failed to affect any of the parameters studied.

These results suggest that cholineretic agonists and antagonists influence mucosal cytoprotective mechanisms possibly through stimulation and inhibition of mucus secretion. Increasing or decreasing mucosal resistance to CDC was associated with marked effects on the level of fluid secretion. A reduction in the secretory response to bile acids may occur with agents not affecting mucus secretion or mucosal injury.

F77
Chronic potassium loading and cyclic AMP stimulate active potassium secretion in the rat colon
E A FOSTER, G SANDLE, J P HAYSLETT, AND H J BINDER (Department of Internal Medicine, Yale University, New Haven, USA) Controversy persists regarding the mechanism of K secretion that normally occurs in mammalian colon and that is increased by oral K loading and by vasoactive intestinal peptide infusion. To investigate the mechanism of K secretion, we performed unidirectional transmural fluxes with 42K under short-circuited conditions across proximal and distal segments of stripped rat colonic mucosa. Net K secretion Jknet: −0.23±0.05 μEq/h.cm² was present in the proximal segment and net absorption (Jknet +0.58±0.11 μEq/h.cm²) in the distal segment. The addition of 5 mM theophylline markedly increased net K secretion in the proximal colon (Jknet: −0.57±0.07 μEq/h.cm², p < 0.001), mainly by increasing Jknet: (from 0.58±0.05 to 0.95±0.09 μEq/h.cm², p < 0.001) with little change in Jknet: In the distal colon, theophylline produced parallel changes. Chronic K feeding for seven to 10 days stimulated net K secretion in the proximal (Jknet: −0.79±0.17 μEq/h.cm², p < 0.005) and distal (Jknet: −1.54±0.37, p < 0.001) segments. This secretory response was secondary to an increase in Jknet (from 0.58±0.05 to 1.26±0.20 μEq/h.cm², p < 0.001) in the proximal colon. Theophylline further increased net K secretion in the K loaded group (from −0.79±0.17 to −1.63±0.23 μEq/h.cm², p < 0.001) also by predominantly stimulus, inhibiting Jknet.

We conclude that both active absorptive and active secretory processes regulate K balance in the rat colon; K loading stimulates active K secretion; and cyclic AMP also induces active K secretion, which may explain the K loss seen in many diarrhoeal disorders.

F78
Evidence for an endogenous steroid-inducible inhibitor of prostaglandin synthesis in human rectal mucosa
C J HAWKEY (Nuffield Department of Clinical Medicine, Oxford) Some of the anti-inflammatory effects of corticosteroids in ulcerative colitis can be attributed to a reduction in basal prostaglandin synthesis. The mechanism by which this occurs has been investigated.

Radiolmmunoassay methods were used to measure basal synthesis of prostaglandin E2 by rectal biopsies in organ culture and determine the cyclo-oxygenase (prostaglandin synthetase) activity at the end of culture. The rectal biopsies were bisected and the effect of prednisolone investigated with each patient providing
his own control. Prednisolone had no direct pharmacological effect on cyclo-oxygenase activity in homogenates without prior organ culture. In organ culture it produced a progressive dose-dependent inhibition of basal synthesis and cyclo-oxygenase activity. The cyclo-oxygenase inhibition developed after a lag (six hours) and could be prevented by treatment with cycloheximide, suggesting that a period of protein synthesis was required. These changes were not due to an effect on prostaglandin metabolising enzymes.

These data suggest that prednisolone may exert its therapeutic effect in ulcerative colitis by enhancing synthesis of an endogenous peptide inhibitor of cyclo-oxygenase activity. This is the first evidence for a local steroid-inducible cyclo-oxygenase inhibitor and a search for evidence of its existence in other tissues may help in the general understanding of inflammatory processes.

F81
Suppressor cell defect in autoimmune chronic active hepatitis is reversed by prednisolone

J E HEGARTY, K Nouri, A L W F EDDLESTON, AND R WILLIAMS (Liver Unit, King’s College Hospital, London) To investigate the suppressor T-cell defect in autoimmune chronic active hepatitis (CAH) and its modulation by corticosteroids, the ability of concanavalin (Con A) stimulated suppressor cells to inhibit proliferation of immunoglobulin peripheral blood lymphocytes (PBL) has been measured by a haemolytic plaque assay in the following groups.

Normal subjects; 12 patients with autoimmune CAH treated with steroids and azathioprine who were in clinical, biochemical, and histological remission; and the same group of patients in relapse after treatment withdrawal. The number of PBL spontaneously producing immunoglobulin G (IgG) was markedly increased in patients during relapse of CAH (3130/10^6 lymphocytes) compared with the same patients in remission (205/10^6 lymphocytes; p<0.01) and control subjects (412/10^6 lymphocytes; p<0.01). Con-A-stimulated suppressor lymphocytes from patients in relapse did not inhibit proliferation of autologous IgG-producing cells (% suppression=78±SD 48), whereas almost complete suppression was observed in the same patients in remission (% suppression=75±SD 18; r<0.01) and in control subjects (% suppression=84±SD 109; p<0.01).

In experiments to determine the effect of immunosuppressive drugs in vitro, PBL from 15 patients with active disease were incubated with low doses of prednisolone (0.5×10^-7 for 30 minutes at 37°C). These treated lymphocytes showed considerable improvement in suppressor function (% suppression=−22±SD 42 before and +51±SD 158 after prednisolone exposure; p<0.01).

The demonstration that a suppressor cell defect in patients with CAH can be reversed in vitro by concentrations of prednisolone comparable with those found in plasma during standard maintenance therapy provides for the first time a plausible explanation for the effectiveness of corticosteroid treatment of autoimmune disease.
F82
T-lymphocyte subsets in chronic active hepatitis (CAH): analysis with monoclonal antibodies

A FACCINI, H G DE BRUIN, E MARIANI, G F STEFANINI, F MIGLIO, A ASTALDI (introduced by A L W F Eddleston) (Clinica Medica I e Patologia Medica III, Università degli Studi di Bologna; Central Laboratory, Netherlands Red Cross Blood Transfusion Service, University of Amsterdam)
The relative distribution of T cell subsets as defined by the monoclonal antibodies OKT was determined by cytofluorimetric analysis in peripheral blood lymphocytes (PBL) of eight untreated CAH (5 HBSAg- and 3 HBSAg+). The percentage of PBL OKT3+ (directed against a common T cell surface antigen and defining most peripheral T cells) was slightly raised in all patients (HBSAg+ 85±2%; HBSAg- 79±6%; controls 67±8%; P<0.05), whereas the percentage of lymphocytes OKT8+ (directed against an antigen present on the suppressor/cytotoxic T cell subset) was normal (HBSAg+ 18±12%; HBSAg- 16±2%; controls 18±7%). The percentage of lymphocytes OKT4+ (defining an antigen present on inducer/helper cells) was markedly enhanced (HBSAg+ 56±3%; HBSAg- 59±12%; controls 46±6%; P<0.01). This resulted in an increased ratio OKT4:OKT8 as compared with normal subjects. The percentage of lymphocytes OKIa+ (defining an antigen present on B cells macrophages and activated T cells) was normal (HBSAg+ 10±8%; HBSAg- 9±6%; controls 10±5%).

We conclude that the ratio helper:suppressor T cells is significantly altered in CAH patients both HBSAg+ and HBSAg-. Because lymphocytes with suppressor phenotype were normal as absolute numbers, but diminished as relative proportion (OKT4:OKT8), it is likely that the decrease of nonspecific suppressor activity is due to 'dilution' of OKT8+ in the T population (OKT3+), rather than to numerical loss of suppressor OKT8+.

F83
Lymphocytotoxicity against autologous hepatocytes and membrane-bound immunoglobulins (IgG) in chronic active hepatitis (CAH)

G F STEFANINI, R MELICONI, F MIGLIO, M MAZZETTI, M BARALDINI, G GUZZARDI, AND G GASBARRINI (introduced by A L W F Eddleston) (III Cattedra di Patologia Medica, Università di Bologna) We have evaluated membrane-bound IgG and lymphocytotoxic activity of total, T-enriched and T-depleted lymphocytes, using autologous hepatocytes in: (a) 18 untreated CAH: four 'autoimmune' and 14 (hepatitis B virus)-related; (b) five inactive alcoholic cirrhosis; (c) nine subjects with normal hepatic histology. Lymphocytotoxicity was positive in 100% of 'autoimmune' CAH and 72% of HBV-related CAH and was confined to the T-depleted subpopulation in the first group while it was predominant in the T-enriched subpopulation in 80% HBV-related cases. Membrane-bound IgG were present in 67% of group (a) and in none of the other groups. A linear pattern was found in all patients with 'autoimmune' CAH, while in HBV-related CAH patients seven presented a granular pattern, one a linear pattern, and six were negative.

Our data suggest that autologous lymphocytotoxicity in HBV-related CAH is mainly due to T-lymphocytes, while in 'autoimmune' CAH the reaction is confined to 'non-T' lymphocytes and could be mediated by linear membrane-bound IgG.

F85
Autoantibodies against gut peptide-secreting cells: occurrence and meaning

H W JONES, R LENDRUM, JANET MARKS, G F BOTTAZZO, D L SARSON, AND S R BLOOM (Freeman Hospital, Newcastle upon Tyne; Royal Victoria Infirmary, Newcastle upon Tyne; Middlesex Hospital, London; Royal Postgraduate Medical School, London) Evidence is presented that autoantibodies occur against gut peptide secreting cells, and preliminary investigations suggest that they may reflect deficiencies of the corresponding hormones.

Sera from patients with coeliac disease (53), dermatitis herpetiformis (14), Crohn's disease (47), ulcerative colitis (65), irritable bowel syndrome (44), and from subjects without known bowel disorders (45) were tested by indirect immunofluorescence on human 'normal' intestinal mucosa. Twenty sera (5-7%) produced fluorescence with mucosal cells having the distribution and morphology of peptide cells. The latter were identified by 4-layer immunofluorescence. Eighteen of the 20 sera reacted with GIP, glucagon, secretin, or somatostatin cells in varying combinations, while five reacted with GIP cells alone. The antibodies occurred in sera from each of the diagnostic categories. Since most of the sera reacted with GIP cells, plasma GIP responses to a standard test meal were compared in 11 subjects with GIP antibodies and in 11 subjects matched for age, sex, and diagnosis but without antibodies. Fasting and two-hour postprandial GIP levels were significantly lower in the group with autoantibodies (P<0.02).

If these antibodies are confirmed to be markers of hormone deficiency then new approaches to the physiology of gut peptides will become possible.
Comparison of cell-mediated immunity (CMI) to gluten fraction III (GFIII) in the peripheral blood and jejunal mucosa of patients with coeliac disease (CD)

P D HOWDLE, F G SIMPSON, A W BULLEN, AND M S LOSOWSKY (Department of Medicine, St James’s University Hospital, Leeds) It has been suggested that CMI to gluten may play a part in causing the mucosal lesion in CD. Peripheral blood leucocytes (PBL) sensitised to GFIII can be detected in coeliac patients, being more easily detectable in patients after commencing a gluten-free diet (GFD). There is also evidence of CMI to GFIII in coeliac mucosa, detectable in untreated patients and reversed in individual patients by treatment with GFD. These findings could be explained by the suggestion that in untreated patients gluten-sensitive lymphocytes are sequestered in the gut, in response to dietary gluten, whereas when gluten is excluded from the diet a higher proportion of these lymphocytes are present in the blood.

To test this hypothesis we have simultaneously assessed CMI of PBL and jejunal mucosa to GFIII in eight untreated and nine treated coeliac patients. When CMI of PBL and jejunal mucosa was compared in all patients there was a significant negative correlation (\( r_s = -0.61, p < 0.01 \)). This supports the above hypothesis that when immunity to GFIII in the peripheral blood is easily detectable that in the jejunal mucosa is less marked, owing to a redistribution of sensitised lymphocytes in response to removal of antigenic stimulus from the gut lumen.

Antigliadin antibodies detected by a modification of the antireticulin antibody test in coeliac patients and their first-degree relatives

D J UNSWORTH, A ELLIS, E J HOLBOROW, R B MCCONNELL (MRC Immunology Group, Bone and Joint Research Unit, London Hospital Medical College) A new, simple immunofluorescent test (IFT) for antigliadin antibodies (AGA) has been developed after the observation that wheat gliadin binds selectively to reticulin in mammalian tissue sections to detect AGA in patients' sera by indirect immunofluorescence. In a preliminary survey, all of 32 children with coeliac disease who were ingesting gluten at the time of testing were positive for AGA by this method.

The sera of a group of coeliac patients and their first-degree relatives have been tested. Nineteen out of 20 (95%) patients who were on a normal diet at the time the blood sample was taken were positive compared with four out of 35 (11%) who were on a gluten-free diet. Four out of six relatives with subtotal/total villous atrophy gave positive results, but only two out of 64 with a normal biopsy. Thus there is a much smaller frequency of false positives compared with the antireticulin antibody test, which has also been used as a screening test to determine who should be biopsied in at-risk populations.

Leucocyte migration inhibition (LMI) test in coeliac disease: a reappraisal

F G SIMPSON, H P FIELD, P D HOWDLE, D A F ROBERTSON, AND M S LOSOWSKY (St James’s University Hospital, Leeds) The LMI test with gluten antigens has been used in coeliac disease to provide evidence of cell-mediated immunity to gluten in blood and in jejunal biopsies. We have previously shown that in jejunal mucosal biopsies cultured with gluten, puromycin fails to inhibit production of leucocyte inhibitory factors, suggesting that these are not lymphokines, and we have therefore re-examined the LMI test using peripheral blood leucocytes.

Migration inhibition tests were performed in 10 coeliacs and six controls using leucocytes from whole blood and purified white blood cell populations. Mononuclear cells showed no inhibition, but polymorphonuclear leucocytes gave results similar to and correlating with the test on whole blood \( (r = -0.556, p < 0.05) \). Polymorphs with added T or B lymphocytes gave similar results to both whole blood and polymorphs alone. The addition of puromycin had no effect on migration indices using whole blood. Leucocytes from normal individuals, incubated with serum from coeliac patients and washed, then showed significant inhibition of migration when incubated with gluten.

These results suggest that the LMI test in coeliac disease is not a measure of T lymphocyte-mediated response to gluten but depends on a humoral factor, possibly cytophilic antibody, acting on polymorphs.

Endoscopic removal of gastric phytobezoars

D T STEIN AND B T STONE (Division of Gastroenterology, Palo Alto Veterans Administration Medical Center) Eleven patients with 13 gastric phytobezoars were encountered over a 15-month period. Barium contrast studies failed to detect the bezoar in 55% (6/11), while all concretions were evident at endoscopy. The average time interval between radiograph and endoscopy was 15 days. Gastric, duodenal, or marginal ulcers were noted at endoscopy in 45% (5/11), but none was detected on radiographs. Various forms of medical therapy were unsuccessful in eliminating the bezoars (low fibre diet, 1/1; enzymes, six; fragmentation, three; metoclopramide, one). Two patients were treated surgically and two were lost to follow-up. Nine bezoars in the remaining seven patients were removed completely from the stomach by suctioning the fragmented concretion through a large channel endoscope (Olympus GIF-1T or TCF-1S). Bezoars were first fragmented with a water-pik, biopsy forceps, or snare and then suctioned through the endoscope. Treatment sessions lasted an average of 50–60 minutes and were well tolerated. Three patients required two treatment sessions for total removal while four patients required only one session. No complications or failures were encountered. Symptoms were not usually eliminated by evacuation of the bezoar. Endoscopic removal of bezoars offers an attractive alternative to surgery or long-term medical therapy.

Incidence and specificity of anal lesions in Crohn’s disease

I R G JONES AND L E HUGHES (Department of Surgery, Welsh National School of Medicine) This paper reports a detailed prospective study of the anorectum in 224 patients presenting to, or being followed-up in, a gastroenterology clinic to determine the incidence of ‘Crohn’s anal’ lesions as defined by Hughes (1978). Eighty-four patients with Crohn’s disease, 40 patients with ulcerative colitis, and 100 controlled patients (with GI symptoms but...
no evidence of IBD) were studied. Lesions were classified into a primary Crohn's lesion, secondary Crohn's lesions, equivocal lesions, and incidental conditions. The incidence of classical Crohn's lesions was 80%, 2.5% of which were colonic involvement. (15% and 6% respectively). Incidental lesions were also common in colitis and control groups. The incidence of the various primary lesions was similar whatever the site of the Crohn's disease, but secondary lesions were more common with colonic involvement.

The study showed that Crohn's lesions can be differentiated from incidental conditions in most cases, but equivocal lesions can present diagnostic difficulty in both ulcerative colitis and other GI conditions. Secondary complications of anal Crohn's disease are commoner with colonic involvement.

PF3 Review of methods for assaying unconjugated bilirubin (uBr) in human bile: accurate measurements obtained by thin layer chromatography (TLC)

M K DUTT, BARBARA MURRAY, AND R P H THOMPSON (Gastrointestinal Research Unit, Rayne, Institute, St Thomas's Hospital, London) The accurate estimation of biliary uBr is crucial to investigating both pigmentation and cholesterol gall stone formation, since uBr may seed cholesterol stones, but estimates vary widely, from 1<15% of total bilirubin. Validated HPLC techniques are unavailable, so we have critically reviewed other simpler methods and obtained accurate TLC measurements.

(1) Total minus 'direct' bilirubin methods: uBr only roughly measured (4<25%;
Ostrow, 1967). (2) Separating uBr before measurement: (a) Chloroform extraction; efficiency increased as pH decreased (confirms Castaldo, 1947; Ostrow, 1970). Nevertheless, methods for serum using pH 7-8 have been applied to bile (Feverly, 1977), underestimating uBr three to six-fold. TLC confirmed chloroform extracts contained, 79-6±13-3% (mean±SD) conjugated bilirubin (cBr) (compare Feverly, 1977; Ostrow, 1978). (b) Therefore acid extraction and correction for cBr would reasonably estimate uBr. We found 79%
8-0±1.7 in gall bladder bile (n=12). (c) Separation by TLC without precautions against oxidation (Boonyapisit, 1976). Using micellar uBr we found recoveries were only 25±7±11±4% (d) Methylesterification before TLC prevents dipyrrrole exchange and extraction is complete. We measured absolute uBr levels taking stringent precautions against oxidation; uBr recovery=68±4±2±1%;
calibration curve (micellar uBr) linear over 0.5-10 uBr applied; cv 7±6%
(n=5). In gall bladder bile %=uBr was 2-76±0-84 (n=12) (compare 16).

Using methods 2a-d uBr varied from <1-15% of total bilirubin, as in the literature, but corrected for extraction pH, cBr co-extraction, and oxidation, %=uBr was 2-5 which agrees with rough estimates from (1) and (2)b and supports our proposed technique (section 2d).

PF4 Long-term results of polyvinyl alcohol (Ivalon) sponge for rectal prolapse in young adults

P B BOULOS, S J STRYKER, AND R J NICHOLLS (St Mark's Hospital, London) The results of Ivalon rectopexy for rectal prolapse have been reported mainly in elderly patients, but long-term follow-up is difficult in this group because of the short life expectancy. Moreover, little is known on the outcome of Ivalon implantation on sexual function, fertility, and late malignancy, which can be better studied in young patients.

Between 1961 and 1975, 32 patients under the age of 40 years were treated without morbidity or mortality. Six were lost to follow-up and 26 were recalled for clinical evaluation by a standard protocol. There were 17 females and nine males (aged 13 to 40 years) who had been treated five to 20 years (average 11 years) previously. Recurrence developed in five patients (19%) and three required further surgery. Fifteen of 20 patients (75%) with preoperative disturbances of continence experienced sustained improvement after rectopexy. There was no change in bowel or bladder function after this operation. All males retained normal erections and ejaculation. Six females tried to conceive but only three were successful. No pelvic malignancy occurred, but one female patient developed breast carcinoma.

This longer follow-up yielded a higher recurrence rate than previously reported. No long-term complications were encountered, but the effect on female fertility requires further study.

PF5 Randomised trial to compare photo-coagulation with rubber band ligation for treatment of haemorrhoids

M R B KEIGHLEY, M M HARES, F GRECA, E NEVIAH, N S AMBROSE, AND J ALEXANDER-WILLIAMS (Department of Surgery, General Hospital, Birmingham) Infrared coagulation (IC) has been claimed to be effective treatment for haemorrhoids. The instrument tip is heated by an infrared beam and when placed on the rectal mucosa produces a localised burn.

We have compared IC with rubber band ligation (RBL) in a prospective randomised trial of 255 patients with haemorrhoids. One hundred and twenty-three patients with haemorrhoids were treated by RBL and 132 by IC. After RBL one patient had a secondary haemorrhage requiring transfusion and after IC one patient had anal pain. At four months, rectal bleeding persisted in 26% of patients after IC compared with 19% after RBL and prolapse persisted in 29% of patients after IC compared with 15% after RBL (not significant). The mean time required to treat patients was less with IC than RBL. More patients required further treatment after IC (n=38) than after RBL (n=20). Two of 10 patients with third degree haemorrhoids treated with RBL required operation compared with four of six patients with third degree haemorrhoids treated by IC.

This study indicates that IC is almost as effective as RBL for the treatment of first and second degree haemorrhoids but is not recommended for third degree haemorrhoids.

PF6 Simplified intravenous nutrition using intralipid based mixtures in a 3-litre bag

W R BURNHAM, P HANSRANI, C E KNOTT, J A COOK, S S DAVIS, AND M J S LANGMAN (University Department of Therapeutics and Department of Pharmacy, City Hospital, Nottingham, and the University Department of Pharmacy, Nottingham) The aim of this project was to develop an intralipid-based intravenous feeding mixture which would simplify nutritional support for patients with gastrointestinal (GI) disease. Tests of emulsion stability were performed on lipid particles mixed with other nutrients in proportions appropriate for such patients. The mean particle size (MPS) in the mixture
(measured by Coulter counter) was 1.00 μg after 12 hours at 4°C; the value for unmixed intralipid was 0.94 μg. Some slight increase in MPS was seen after 48 hours at 4°C. Electrophoretic mobility measurements showed no permanent changes in the outer phospholipid layer of intralipid particles after mixing. Divalent cations were potent destabilisers of emulsion mixtures.

The emulsion mixture used clinically contained 2800 non-protein K calories, 141 g nitrogen, and adequate electrolytes and vitamins in a 3-litre bag. Twenty patients were fed intravenously (mean 14 days); 10 of them using only peripheral veins (mean 12 days). All patients except one severely ill were maintained in positive nitrogen balance. Other nutritional parameters improved also, and no serious side-effects of treatment occurred. This method of intravenous nutrition has proved safe, effective, and more simple to manage than those used previously.

PF7
Layer separation from human gut for the study of regulatory peptides in the neuroendocrine system (NES)

G-L FERRI, A HARRIS, L PROBERT, A M J BUCHAN, P J MARANGOS, T E ADRIAN, M A GHATEI, S R BLOOM, AND J M POLAK (Histochemistry Unit, Royal Postgraduate Medical School, London; National Institute of Mental Health, Bethesda)

The three-dimensional pattern of the various components of the gut NES and their differential content of endocrine/neural peptides has been little investigated in man. From 10 adults (operated on for carcinoma) and six neonates (cot deaths) we separated (by EDTA incubation and microdissection) samples of normal lower gut into its main layers: mucosa, lamina propria, submucosa, and muscle. Both endocrine cells and neural elements were ultrastructurally unaffected by the procedure. Immunocytochemistry and histochemistry showed the three-dimensional organisation of the peptidergic, adrenergic, and cholinergic innervation of each individual layer. Radioimmunoassay confirmed the reliability of the separation method and its suitability for quantitative estimations by demonstrating <1% of the total content of VIP (neural peptide), >95% of enteroglucagon (confined to endocrine cells) in the mucosal fraction (n=6). The recovery of neuron-specific enolase, a general marker for all the components of the gut NES, was 94±7-2 (SEM) % from separated layers compared with whole gut (n=6). Thus all the components of the gut NES appeared to be preserved in their integrity and organisation in each single layer. This approach provides a powerful tool for the detailed study of the gut NES in human physiology and disease.

PF8
Peptidergic nerves are distinguishable by the appearance and size of their large granular secretory vesicles

L PROBERT, J DE MEY, AND J M POLAK (Histochemistry Unit, Royal Postgraduate Medical School; Laboratory of Oncology, Janssen Pharmaceutica, Beerse, Belgium)

The discovery of a massive peptidergic innervation within the gut is consistent with the demonstration of morphological heterogeneity within the enteric p-type (peptidergic) nerves. These peptides are known to play a part in numerous pathological conditions. To understand the functions of these nerves it is necessary to be able to characterise them by electron microscopy. Using an immunogold labelling technique substance P (SP) and VIP-immunoreactive nerves can be routinely immuno-stained and distinguished in conventionally fixed tissue. Guinea-pig colonic tissue was fixed in 3% buffered glutaaldehyde and embedded in Araldite. Ultrathin sections were immunostained using specific antisera at dilutions 1/8000 (SP) and 1/6000 (VIP). SP- and VIP-like immunoreactivity was localised within predominantly spherical, large, dense-cored secretory vesicles present in distinct subpopulations of p-type neurons. The immunoreactive fibres were distinguishable by the size and appearance of their vesicles, those immunoreactive for SP being of medium electron density measuring 84±17 nm and those immunoreactive for VIP being slightly denser and measuring 92±22 nm. Other p-type subpopulations remained unstained by either SP or VIP antisem. This situation is analogous to the gut endocrine cells, which can now be recognised functionally by morphology alone in both health and disease.

PF9
Do we have valid markers for radionuclide gastric emptying studies?

G JOHN, R JIAN, J J BERNIER (Research Unit on Pathophysiology of Digestion, Hospital Saint-Lazare, Paris)

Measurement of gastric emptying of solid-liquid meals by isotopic technique requires specific-valid markers for lipid, solid, and aqueous phases. The present study was designated to validate in physiological conditions these three kinds of marker: (a) selenium-75 glycerol triether, a new lipid-marker; (b) technetium sulphur colloid bound to egg white, a solid-marker easy to prepare but little used; (c) indium DTPA regarded as a reliable liquid-marker.

Ten subjects ate a solid-liquid meal labelled with these markers. Gastric intubation allowed samples every 30 minutes for three hours. In each sample technetium and indium were counted in solid and liquid phases separated by centrifugation (1600 g x 20 min) and filtration. Selenium was counted on lipid and non-lipid phases separated by toluene-ethanol extraction. Immediately after meal ingestion, 97±2% (mean ± SEM) of selenium was recovered in lipids and 92±7% of technetium in solids. The same percentages were obtained in following samples. Percentage of indium recovered in liquids was 74±9% after mean ingestion and decreased progressively with time (57±7% at 3 h).

Thus, in physiological conditions, selenium glycerol triether and technetium bound to egg white are very specific lipid and solid markers respectively, whereas indium is not a reliable liquid marker. This among other factors may explain differences of liquid half-emptying time between isotopic and intubation techniques.

PF10
Activity of monoclonal antibodies on colonic sections using immunohistochemical techniques

P J FINAN, R M GRANT, E LENNOX, N M BLEEHEN, AND M H THOMPSON (MRC Clinical Oncology and Radiotherapeutics Unit and Laboratory of Molecular Biology, Cambridge)

Monoclonal antibodies with their specificity and homogeneity are replacing conventional antisera in many fields of medical research. Present methods of screening the antibodies produced by a single fusion show little about their site of activity. Immunohistochemical methods have been used to look at the distribution of antibody activity on sections of interest.

Using indirect immunofluorescence on frozen sections of colonic tissue, eight rat
monoclonal antibodies, isolated after immunisation with a human colonic carcinoma membrane preparation, showed activity on various constituents of normal colon—smooth muscle, goblet cells, and epithelial surface. Two showed specific fluorescence on malignant colonic epithelium. Only two of the eight antibodies showed activity on paraffin sections of the same tissue, using an indirect immunoperoxidase technique. One stained all normal colonic epithelium, the other showing maximal activity on malignant colonic tissue. This second antibody has recognised an antigen present in a consecutive series of 30 carcinomas of the colon.

It is concluded that screening of monoclonal antibodies on tissue sections of interest, using routine immunohistochemical techniques, is a valuable addition to the screening methods at present in use.

PF11
Distribution of antitumour reactivity in the regional lymph nodes of colorectal cancer patients

G H HUTCHINSON, M O SYMES, AND R C N WILLIAMSON (University Department of Surgery, Bristol Royal Infirmary) In vitro studies of both lymphocyte and antitumour cytotoxicity and blastogenesis in response to autologous tumour antigens have produced conflicting reports concerning lymph node immunoreactivity against autologous colorectal carcinoma cells.

Using a two-hour $^{51}$Cr release assay, the cytotoxic reactivity of lymph nodes ($n=24$) draining colorectal carcinomas ($n=17$) was studied against tumour target cells from the same patient. Twelve nodes (50%) from 11 patients (65%) showed cytotoxicity. Ten of these nodes were within 5 cm of the primary tumour, and there was a direct correlation ($p<0.001$) between the level of cytotoxicity and proximity of the node to the tumour. Three lymph nodes within 5 cm of the tumour produced no cytotoxicity, and each of these contained metastatic tumour. The other 21 nodes were histologically tumour-free.

Since the cytotoxicity of lymphocytes infiltrating colorectal cancers can be increased by repeated washing, their reactivity may be blocked, possibly by membrane-adherent tumour-associated antigen. In contrast, it appears that lymph node immunoreactivity is greatest in those nodes closest to the primary tumour. However, comparable blocking of this reactivity occurs when tumour invades the lymph node.

PF12
Cell-mediated immune reactivity in peptic ulcer disease

A P BURFORD-MASON AND J M T WILLOUGHBY (Departments of Pathology and Medicine, Lister Hospital, Stevenage) Seventeen patients with peptic ulcer disease were compared with normal controls for cell-mediated reactivity to Candida albicans by skin testing, lymphocyte transformation, and leucocyte migration inhibition. There was no significant difference in skin reactivity, either on first testing or on a second occasion one month later. Uptake of $^{125}$I-deoxyuridine by lymphocyte cultures after six days' incubation was depressed in the patients ($p<0.002$). Suppressor activity, calculated from the change in radioisotope uptake after cultures had been preincubated for 24 hours was also diminished ($p<0.01$). Leucocyte migration inhibition was likewise less in patients than controls ($p<0.01$) and correlated with suppressor activity ($p<0.01$).

Since we have found peripheral blood T-lymphocyte counts to be within the normal range in such patients, we conclude that their disease introduces a new suppressive factor, perhaps a product of the inflammatory process, in response to which intrinsic suppressor activity is partially or wholly switched off. This could be seen as an amplifying mechanism whereby an appropriate defensive response may be mounted.

PF13
Causes of cirrhosis of the liver in Wiltshire (10 years' survey)

SARAH KNOTT AND MILENA LESNA (Salisbury General Infirmary) The aetiology of hepatic cirrhosis is not fully understood and it may vary in different geographical areas. The incidence of alcohol abuse as a cause of cirrhosis has been reported as 20% in a necropsy review from Glasgow (1973), 65% in a recent London biopsy series (1976), and 83% in the Boston study (1963).

Results of a local survey of cirrhosis of liver diagnosed in Salisbury General Infirmary over the period 1970–80 are reported. The hospital serves a rural population of approximately 180,000 and has no specialised liver unit. A clinico-pathological review of posthumous and liver biopsy samples showed 66 cases of cirrhosis: 35 were alcoholic cirrhosis, six probably alcoholic, four haemochromatosis, three secondary biliary cirrhosis, two primary biliary cirrhosis, two probably post-hepatitic, one chronic active hepatitis, one sclerosing cholangitis, and 12 cryptogenic.

Our results show that in the majority of cases (62%) alcoholic abuse has been a major contributing factor. More than one possible cause was found in some instances and a considerable proportion of patients suffered from diabetes.

PF14
Are gamma glutamyl transpeptidase (GGT) and mean corpuscular volume (MCV) useful markers of excessive drinking among pregnant women?

I G BARRISON, B SAMPSON, J T WRIGHT, I M MURRAY-LYON (Gastrointestinal Unit and Departments of Chemical Pathology and Obstetrics and Gynaecology, Charing Cross Hospital and Medical School, London) The combination of GGT and MCV detects over 60% of heavy drinkers. GGT levels decrease in teetotallers during pregnancy and the MCV may drop owing to iron deficiency. The aim of this study was to establish the value of these tests in screening for heavy drinking during pregnancy.

Drinking, dietary, and drug histories were taken from 450 women in the first trimester, in all of whom GGT and MCV were measured. The women were classified into teetotallers, light drinkers (0–40 g/day), and heavy drinkers (>40 g/day). Two subgroups of 100 of the same women (chosen at random) had GGT and MCV repeated in the second and third trimesters. Twelve out of 16 women in the "heavy" group had a raised GGT in the first trimester, but only one out of the six who continued to drink heavily had a persistently raised GGT for the rest of the pregnancy. None of the 16 heavy drinkers had a raised MCV (>95 fl) during their pregnancies, although 6/16 had previously had an MCV >100 fl documented.

We conclude that GGT is a useful marker of heavy drinking only in the first trimester of pregnancy and that MCV is of no value in screening pregnant women for excessive drinking.
Fibromatosis and desmoid tumours in Gardner’s syndrome

J M Hay and M B Bruce (Palmerston North Hospital, New Zealand) Rectal bleeding in a 26-year-old female led to diagnosis of familial polyposis coli affecting two out of three siblings and their father, all asymptomatic. All have had total colectomy, the father having established but operable malignancy at surgery.

One sibling had a large unsuspected infiltrative intra-abdominal tumour at colectomy, initially thought malignant but proving to be a fibromatous but benign infiltrating tumour. She and the original patient have subsequently developed large desmoid tumours in the abdominal incisions, the latter proving on excisional reoperation to have large fibromatous intramesenteric masses also. These are well displayed by photographs and CT scan showing intestinal involvement in both patients and ureteric obstruction in one. Gardner’s syndrome comprises: familial polyposis coli; osteomatosis and dental abnormalities; multiple epidermoid cysts; infiltrating fibromatous tumours and desmoids. The latter predominate in this family and are life threatening by encroachment on ureter, bowel, etc.

Surgical extirpation is usually advised in desmoids but rarely possible in mesenteric and extraperitoneal situations and recurrence is likely. Radiotherapy is probably ineffective but recent work suggests that tumours regress using drugs which affect metabolism of cyclic AMP.

Also mentioned are genetics of the condition and management of extracolonic polyps.