The British Society of Gastroenterology

The Autumn Meeting of the Society was held from 22 to 24 September 1982 at the University of Leeds under the presidency of Professor C G Clark. One hundred and fifty-three communications (including 29 posters) were selected for presentation in the scientific programme on September 23 and 24; the abstracts are printed below.

POSTERS
WP1–WP29

WP1
Peptide-containing nervous system of the gut in three forms of megacolon
A E BISHOP, G P MCGREGOR, B D LAKE, D M PRESTON, S R BLOOM, AND J M POLAK (Departments of Histochemistry and Medicine, Hammersmith Hospital, Department of Pathology, The Hospital for Sick Children, Department of Medicine, St Mark’s Hospital, London) It has been established that the peptide-containing nerves of the gut show distinct abnormalities in certain diseases. In the present study, the techniques of immunocytochemistry and radioimmunoassay have been used to investigate these nerves in surgical specimens from patients with three forms of megacolon: congenital (n=8), acquired (n=10), and idiopathic (n=6).

A marked reduction in peptide-containing nerves was observed in both congenital (Hirschsprung’s disease) and acquired (Chagas’ disease) megacolon. In Hirschsprung’s disease the loss of peptide-containing nerves was largely in proportion to the length of the aganglionic segment. In Chagas’ disease, however, where the neuronal degeneration in the gut is diffuse, the extent of the reduction in peptide-containing nerves was variable. Radioimmunoassay demonstrated a decrease in the content of neuropeptides in both diseases. For example, the content of VIP was reduced from 142±18 pmol/g wet weight of tissue in normal neonatal bowel to 57±8 pmol/g in aganglionic bowel. In contrast, no abnormality of peptide-containing nerves could be detected in idiopathic megacolon.

These results provide new means for the investigation of the pathogenesis of megacolon and indicate that the underlying abnormality in idiopathic megacolon does not involve the peptide-containing component of the enteric nervous system.

WP2
Localisation of distinct sub-populations of gastrin-containing secretory granules in the mammalian gastrointestinal tract using a new double immunogold staining method
I M VARNDELL, F J TAPIA, J DE MEY, N YANAIHARA, S R BLOOM, AND J M POLAK (Departments of Histochemistry and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, Department of Life Sciences, Janssen Pharmaceutica, Belgium, Department of Bio-Organic Chemistry, Shizuoka School of Pharmacy, Shizuoka, Japan) Two bioactive molecular forms of gastrin are known to occur in endocrine cells in the mammalian gut. Gastrin 17 (G17), the carboxy terminal heptadecapeptide of big gastrin (G34), is the predominant molecular form in the human gastric antrum and some authors have speculated that G17 is contained within the electron-lucent vesicles which are characteristic of antral G cells. In addition to the electron-lucent vesicles there is a subpopulation of smaller granules with an electron-dense core and a closely apposed limiting membrane. We have attempted to localise gastrin immunoreactivity within these two distinct subpopulations in the gastrointestinal tract of cat and man using a new double immunogold staining method. The double immunogold staining procedure is based on the conjugation of colloidal gold (20 or 40 nm) to immunoglobulins which recognise the primary antisera (rabbit (R) anti-N-terminal gastrin 34 and guinea-pig (GP) anti-N-terminal gastrin 17). The primary antisera were visualised using goat anti-R40 nm and goat anti-GP20 nm. Using N-terminal G17 antisera we have been able to demonstrate specific immunoreactivity in the electron-lucent vesicles of mammalian antral G cells and also in gastrinomas which are known to secrete predominantly G17. In addition, using N-terminally directed antisera to G34 we have visualised immunoreactivity in the electron-dense secretory granules of intestinal G cells in man (160 nm) and cat (280 nm). Both G17 and G34 immunoreactivities have been demonstrated simultaneously in the electron-dense granules which coexist with the electron-lucent vesicles in antral G cells.

WP3
Pharmacological properties of two new sulphasalazine analogues
J E LENNARD-JONES, J H BARON, ROSALIND P CHAN, D J POPE, A P GILBERT, AND P J SACRA (St Mark’s Hospital, London, St Charles Hospital, London, Biorex Laboratories Ltd., London) Circulating sulphapyridine is the main cause of unwanted side-effects with sulphasalazine, whereas the 5-aminosalicylic acid (5ASA) component may be the active moiety. Two analogues have been synthesised in which sulphapyridine has been replaced by either 4-aminobenzoylglycine (ABG) or 4-aminobenzoyl-p-alanine (ABA) to yield balsalazine and sulphasalazine respectively. Both new compounds are crystalline, non-hygroscopic stable dihydrates, highly soluble in water (up to 22% W/V). Acute toxicity of balsalazine and sulphasalazine was not demonstrable in rats and mice with single doses up to 2.4 g/kg body weight. Chronic toxicity of balsalazine was not demonstrable in dose levels up to 1 g/kg in rats and 0.5 g/kg in ferrets over 90 days. Metabolic studies in rats showed that recoveries of 5-ASA in urine and faeces were similar for sulphasalazine, hipsalazine, and balsalazine. In normal human volunteers only trace amounts of unchanged hipsalazine and balsalazine were excreted in urine and faeces after a single oral dose of 2 g. Two-thirds of the 5-ASA in sulphasalazine and hipsalazine, and half of that in balsalazine appeared in the faeces. Total recoveries of 5-ASA in faeces and urine were over 80% with each drug. There was a marked difference in the excretion pattern of the carrier molecules sulphapyridine (faeces 6%, urine 85%) and...
ABG (faeces 8%, urine 45%) compared with ABA (faeces 74%, urine 19%). Serum concentrations of hispanalazine, balsazaline, ABA and 5-ASA were below the limits of detection (−2 μg/ml), mean levels of ABG did not exceed 3 μg/ml compared with free sulphasalazine which reached a mean level of 24 μg/ml. These two analogues appear to be suitable for therapeutic trial.

WP5 Prediction and treatment of severe acute pancreatitis by peritoneal lavage

A P CORFIELD, M J COOPER, R C N WILLIAMSON, AND A V POLLOCK (Department of Surgery, Bristol Royal Infirmary, Bristol, and Scarborough Hospital, Scarborough) One hundred and fifty-one patients with raised serum amylase (>1200 IU/l Phadebas) were entered into a prospective controlled trial to evaluate reports that peritoneal lavage may predict, and improve survival in severe acute pancreatitis. There were 78 males and 73 females with a mean age of 60.8 years, the majority (64%) having gallstone-related pancreatitis. Two predictive criteria of severity on admission were assessed; hypoaemia (PaO₂ <7.98 kPa) and toxic peritoneal broth. One or both criteria were fulfilled by 39 patients of whom 12 died (31%) and eight developed other major complications (21%). Two of the 112 with predicted mild disease died (2%) and eight developed major complications (8%). The overall accuracy of these predictive criteria is 81%. Patients with predicted severe disease (n=39) were randomised to receive therapeutic lavage with hourly cycles of 2 l dialysate for 72 hours (n=16) or to act as controls (n=23). The following results show figures for control first and lavage second: benign course, 11, 8; major complications, 4, 4; death, 8, 4.

An accurate guide to the likely severity of an attack of acute pancreatitis is provided by the predictive criteria, but the value of therapeutic peritoneal lavage remains unproven.

WP4 Imbalance of prostacyclin and thromboxane synthesis in Crohn’s disease

C J HAWKEY, F K KARMELI, AND D RACHMILEWITZ (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, and Hadassah University Hospital, Jerusalem, Israel) Rectal mucosa from patients with ulcerative colitis in relapse (but not remission) synthesises excess quantities of prostanooids in organ culture, but data are lacking for patients with Crohn’s disease.

Thirty rectal biopsy specimens from British patients (23 Crohn’s disease, seven normal) were placed in organ culture for 24 hours. The accumulation of prostaglandin (PG)E₂, 6 keto PGF₁α, and thromboxane (TX)B₂ was measured by radioimmunoassay.

Synthesis of TXB₂ by uninflamed mucosa from patients with Crohn’s disease (0.90 ng/mg, 0.11−3.52 ng/mg, median and range, n=11) was greater than by normal mucosa (0.18 ng/mg, 0.15−0.74 ng/mg, n=7, p<0.05) and was similar to that seen with inflamed mucosa (0.66 ng/mg, 0.21−3.76 ng/mg). The groups did not differ in the synthesis of 6 keto PGF₁α, but the ratio of 6 keto PGF₁α to TXB₂ was reduced in Crohn’s disease (0.60−0.88−2.33) compared with normal (1.48−0.64−2.78, p<0.02). Inflamed mucosa synthesised more PGE₂ (4.67 ng/mg, 1.48−20.44 ng/mg, n=12) than uninflamed mucosa (2.22 ng/mg, 0.88−12.75 ng/mg, n=11, p<0.02).

We conclude that there is an imbalance of prostacyclin and TXB₂ synthesis in Crohn’s disease even in the absence of inflammation. The consequences may include vasoconstriction, platelet aggregation, reduced suppressor cell activity, and possibly diminished ‘cytoprotection’.

WP6 Adaptation of the shortened gut: increased numbers of sialomucin-containing goblet cells

I O OLUBUYIDE, R C N WILLIAMSON, I B BRISTOL, AND A E READ (University Departments of Medicine and Surgery, Royal Infirmary, Bristol) Both clinical and experimental studies have shown hyperplasia of the small bowel remaining in continuity after jejunoe ileal bypass, and the colon may contribute to the compensatory response. Numerical changes in the different types of epithelial cell have not been identified, however. Adaptation of the goblet cell population was therefore studied in male Sprague-Dawley rats (n=40) weighing 75−246 g (SEM) and randomised to receive 85% end-to-side jejuno ileal bypass or sham bypass (jejunal transection, ileotomy, and resuture). At 36 weeks jejuno ileal bypass increased the length and wet weight of the duodenum by 38−55% and of the large intestine by 13−25% (p<0.05−0.001). In the duodenum and functioning jejunoleum, villi were 43−63% taller and crypts 41−69% deeper (p<0.02−0.001). Jejunoleal bypass also increased crypt depth in the distal colon by 24% (p<0.001). Goblet cells containing specific acid mucins were differentiated histochemically, using high iron diamine-alcian blue. Irrespective of operation, sulphomucins predominated throughout the gut. Jejunoleal bypass increased the number of sulphomucin-containing goblet cells only in ileal villi (by 16%) and distal-colon crypts by 27%. By contrast, sialomucin cells were two to three times more common both in the distal colon (p<0.02) and in the villi and crypts of the functioning jejunoleum (p=0.04−0.002).

Adaptation to jejunoleal bypass involves all the residual functioning intestine and includes goblet-cell hyperplasia. Sialomucin-containing cells are increased disproportionately.

WP7 Effect of sodium and acetyl-salicylates on bile flow in man

M J COOPER AND R C N WILLIAMSON (University Department of Surgery, Bristol Royal Infirmary, Bristol) We have previously shown that sodium salicylate is a potent choleretic in the Rhesus monkey, but were unable to confirm the alteration of lithogenicity observed in dogs after administration of lysine acetyl-salicylate.

To investigate the possible value of salicylates in the treatment of biliary disease, five patients with indwelling T-tubes were studied. T-tubes were clamped for 48 hours to restore the enterohepatic circulation before study. Bile was then collected over a one-hour baseline, and 1.8 g sodium salicylate and 1.8 g acetyl-salicylate were administered p.o. on consecutive days; collection was continued for a further two hours. Baseline bile flow was 7.07±0.16 ml/kg/24 h (mean±SEM) and increased to 11.46±0.43 ml/kg/24 h (p<0.01) with sodium salicylate and to 9.67±0.44 ml/kg/24 h (p<0.001) with acetyl-salicylate. Baseline biliary acid secretion (0.26±0.02 mmol/kg/24 h) was unchanged after either drug, confirming that the choleretic is bile acid-independent. Baseline secretion of phospholipids...
(0.07±0.01 mmol/kg/24 h) and cholesterol (0.03±0.003 mmol/kg/24 h) was also unchanged after both drugs, indicating no change in lithogenicity; the lithogenic ratio remained at 11.81±0.4. These results demonstrate that both sodium and acetyl salicylates increase human bile flow, but at a lesser order of magnitude than the choleretic seen in dogs or monkeys. Neither agent affects the lithogenicity of primate bile.

WP8
Determinants of cholesterol saturation of fasting gall bladder bile in health
R P JAZRAWI, R M KUFFER, C BRIDGES, A JOSEPH, AND T C NORTHFIELD (Departments of Medicine and Nuclear Medicine, St George's Hospital Medical School, London) Since saturation index is higher for fasting than for postprandial hepatic bile, percentage gall bladder filling may influence saturation index of fasting gall bladder bile. We have therefore developed a simple, rapid scintiscanning technique for assessing this. The conventional measurement of saturation index does not indicate whether a rise is due to excess of cholesterol, or deficiency of bile acid and phospholipid within the gall bladder. We have therefore measured the mass of all three biliary lipids by combining our scintiscanning technique with direct analysis of gall bladder bile. We also measured bile acid pool size by isotope dilution. We studied 12 non-obese healthy male volunteers. After intravenous 99mTc-HIDA, gall bladder and gut activity were measured using two isosensitive scanning heads (anterior and posterior). Gall bladder bile was obtained by nasoduodenal intubation. The concentration of biliary lipids was determined, and Ta-HIDA activity was measured in vitro in exactly the same way as for the in vivo studies. Bile acid pool size was determined by isotope dilution. Percentage gall bladder filling (mean ± SEM) was 54±8%, and was significantly correlated with saturation index (r=0.63, p<0.05). Saturation index was also significantly correlated with cholesterol mass in the gall bladder (r=0.64, p<0.05), but not with bile acid (r=0.40) or phospholipid mass (r=0.03), or with bile acid pool size (r=0.36). We conclude that saturation index of fasting gall bladder bile in health is influenced by the degree of gall bladder filling, and by cholesterol mass in the gall bladder.

WP9
Natural history of chronic active hepatitis
F CARUBBI, M PONZ DE LEON, P DI DONATO, P LORIA, I IORI, AND N CARULLI (Istituto Clinica Medica II, Università di Modena, Italy) A recent long-term trial suggested that the natural history of untreated chronic active hepatitis seems to proceed from an active hepatitis to inactive cirrhosis, with a 27% survival at 10 years, and that prednisolone improves survival. This study, however, dealt with severely ill patients probably not representative of the vast majority of patients with chronic active hepatitis, as pointed out by more recent studies. A detailed review was therefore undertaken of the patients with chronic active hepatitis without cirrhosis admitted in our Institute between 1971 and 74 and subsequently followed up to now. Twenty patients were included in the study (M18, F2) with the following criteria: (1) none was treated with corticosteroids or immunosuppressive drugs; (2) all had a liver biopsy at the first admission, and at least a second biopsy during the follow-up; (3) minimum follow-up was 7.5 years (mean 9.6, range 7.5-11 years).

Results showed that HBsAg was positive in 12 (60%) and remained positive throughout the study except for one patient who seroconverted to the negative state. At the time of diagnosis 14 patients were virtually asymptomatic; two patients had ascites that disappeared with low salt diet and did not reappear, in contrast one patient developed ascites, with other signs of cirrhosis, after six years. Jaundice was present in four patients at the diagnosis but disappeared rapidly during the hospitalisation without reappearing. Oesophageal varices were not present in any patient at the diagnosis and subsequently appeared in three. At diagnosis the biochemical profile showed a modest impairment of the liver function; this, on average, tended to improve slightly during the follow-up. Histology was considered improved in two patients (whose diagnosis became chronic persistent hepatitis), virtually unchanged in 13 (65%), and worsened in five patients (25%), who showed histological features of cirrhosis. None of the patients died and most of them continued their usual work.

We conclude that this long-term follow-up showed that chronic active hepatitis without cirrhosis is a less severe disease than previously reported; chronic active hepatitis shows a protracted clinical course without impairment of the general state in most of the patients. Cirrhosis, however, eventually develops in a definite proportion of these patients. In our opinion, the real benefit of drugs on the natural evolution of the disease has yet to be proved.

WP10
Terpene treatment for gallstones: five years of experience with rowachol 1977-82
W R ELLIS, K W SOMERVILLE, D H ROSE, A T R AXON, AND G D BELL (University Department of Therapeutics and X-ray Department, Nottingham City Hospital and Gastroenterology Unit, General Infirmary, Leeds) We treated 48 cases of radiolucent gall bladder stones with rowachol alone (1-6 capsules daily): nine responded, including 3/42 (7%) complete dissolution (excluding six planned withdrawals), or 8.3 per 100 patient-years. Rowachol did not alter duodenal bile cholesterol saturation (1:36±0.21 SD before, 1:31±0.28 after, n=9). Rowachol (2-3 capsules daily) was combined with suboptimal chenic acid (CDC) dosage – 375 mg/day (A) or 7.5-10 mg/kg/day (B). On dosage A, complete dissolutions were 6/31 (19%) at 12 months and 8/30 (27%) at 24 months. Three patients' biliary symptoms required surgical intervention and one had diarrhoea, nine changing treatment after 12 months. On dosage B, five patients showed progressive dissolution during treatment; stone disappearance occurred in 9/30 (30%) at 12 months and 12/25 (48%) at 24 months. No patient had severe symptoms, one had possible side-effects, and nine elected to discontinue treatment after six to 12 months.

Using Rowachol alone, 6/18 (33%) of ductal stones dissolved in 12 months and 7/17 (41%) in 24 months; no radio-opaque stones disappeared but 6/21 (29%) responded partially within two to three years.

We concluded that Rowachol alone was active, comfortably exceeding placebo dissolution rates (about 0.4 per 100 patient years) for gall bladder stones and comparing favourably with bile acid therapy for duct stones. Tolerance of Rowachol and Rowachol-CDC combinations was excellent; continued biliary pain and adverse effects were rare. Efficacy of combination treatments using suboptimal CDC doses considerably exceeds that of either drug alone and compared well with full-dose bile acid treatment. Since duodenal bile remains saturated, alter-
native mechanisms, as recently suggested, must be proposed for Rowachol’s adjuvant cholelitholytic properties.

WP11
Demonstration of immunoreactive sites of insulin biosynthesis using immunogold procedures
F J TAPIA, I M VARNDELL, J DE MEY, L HEDING, N YANAIHARA, S R BLOOM, AND J M POLAK (Departments of Histochemistry and Medicine, RPMS, Hammersmith Hospital, London, Department of Life Sciences, Janssen Pharmaceutica, Belgium, Novo Research Institute, Denmark, and Shizuoka College of Pharmacy, Japan) The enzymatic cleavage of proinsulin in the Golgi region and secretory granules of the B-cell yields insulin and C-peptide. The secretory granules of the B-cell are of three types, spherical electron-opaque (pale), spherical electron-dense, and crystal-line core granules. We have identified biosynthetic sites of insulin in normal human pancreas (n=4) and insulinomas (n=15) using antidsera to porcine insulin and to synthetic human C-peptide (known to cross-react extensively with proinsulin). Immunoreactive sites were detected at the electron microscopical level using single and double immunogold procedures. C-peptide (proinsulin) immunoreactivity was demonstrated in a subpopulation of spherical pale and electron-dense core granules. Very little immunostaining was observed in the crystalline-cored granules. In contrast, insulin was immunostained in all the granules. Some atypical (non-diagnostic) tumour cells were immuno-reactive to insulin and C-peptide (proinsulin), other atypical cells were found to contain pancreatic polypeptide (n=4). Insulin and C-peptide (proinsulin) were also demonstrated around the Golgi region. These results show for the first time the ultrastructural localisation of proinsulin to a subpopulation of the B-cell granules.

WP13
Dual localisation of PHI in the gut and brain
N D CHRISTOFIDES, Y YIANGOU, G P MCGREGOR, M A GHATEI, K TATEMOTO, J M POLAK, AND S R BLOOM (Department of Medicine, Royal Postgraduate Medical School, London) PHI, the most recently discovered gut peptide, has recently been localised immunohistochemically in the human colon. The aim of this study was to document its precise distribution in the gastrointestinal tracts of three species and to investigate its localisation in the brain. The full gastrointestinal tracts of five rats, six guinea-pigs, and five cats were examined. These were dissected into fundus, antrum, duodenum, jejunum, and colon. In addition, the brains of six rats were dissected into the cortex, hippocampus, mid-brain, brain stem, and cerebellum. Tissues were extracted in 0.5M acetic acid and assayed using a previously described PHI radioimmunoassay. In all three species the lowest PHI concentration occurred in the fundus (<20 pmol/g), levels increasing caudally reaching a peak in the colon (rat 140±13 pmol/g and guinea-pig and cat 360±40 pmol/g). In the rat brain, PHI was found in the cortex (35±4) and hippocampus (35±8 pmol/g) with lower concentrations in the mid-brain (10 pmol/g) and brain stem (±0.6 pmol/g). PHI was undetectable (<0.3 pmol/g) in the cerebellum.

Thus PHI is the last member of the group of peptides with a dual (gut and brain) localisation, and which are thought to have a role as neurotransmitters or neuromodulators.

WP14
Outpatient preparation for colonoscopy by sodium picosulphate
D G KARAMANOULIS, P B BOULOS, AND P R SALMON (Departments of Surgery and Gastroenterology, School of Medicine, University College London, University Street, London) Preparation of patients for colonoscopy involves colonic washouts and requires hospital admission if day facilities are not available. Bowel preparation with oral sodium picosulphate without colonic washout has been successfully used in barium studies of the large bowel but its use in colonoscopy has not been examined. In this study 46 consecutive patients undergoing colonoscopy were randomised to either a test group prepared with sodium picosulphate and low residue diet (without washout enema) the day before colonoscopy or to a control group prepared by a standard regimen consisting of three day low residue diet, purgatives, and washout enemas. The patient’s acceptability was measured by a scoring scale and the endoscopist’s assessment of the bowel cleanliness was described as good, adequate, or moderate.

There were 26 patients in the test group and 20 in the control group. The patient’s acceptability score (0–11 median 4.25) in the test group was significantly better (p<0.01) than in the controls (2–13 median 6.9). In the test group, the bowel cleanliness was good in 14, adequate in four, moderate in eight; in the controls 12, six, two respectively and were not different statistically by χ² test. The haematocrit, urea, and electrolytes before and after bowel preparation in both groups did not show any change demonstrable statistically. These results show the efficacy...
of sodium picosulphate in bowel preparation for colonoscopy and can be recommended for outpatient use.

WP15
Collagenase inhibition in colonic mucosa by proteinase inhibitors
A P JAYARAJ, P R HAWLEY, P B BOULOS, AND C G CLARK (Department of Surgery, School of Medicine, University College London, University Street, London) It has been shown that the colonic mucosa produces collagenase after injury which may be responsible for the breakdown of colonic anastomosis and this is demonstrable by lysis of collagen substrate. This study investigates the possibility of inhibiting collagenase by proteinase inhibitors.

Forty-two male New Zealand white rabbits were randomly allocated into seven equal groups; one group acted as a control and six groups were treated with a single dose of soy or lima bean trypsin inhibitor – SIGMA (1 mg in 2 ml water) administered either intramuscularly, or by instillation into the stomach or into the rectum. After three days, the animals were killed and 2 mm colonic mucosa was removed by tissue punch from each animal. These were explanted on collagen gel plates and incubated for 72 hours. The lysed area on the collagen gel was drawn on tracing paper, cut out and weighed to express lysis in milligrams. The mean areas of lysis in animals treated with soy bean were 20-0±3-2 when given intramuscularly, 20-0±6-0 when instilled into the stomach, 0-1±0-38 when instilled into the rectum and the respective areas in animals treated with lima bean were 4-0±1-8, 15-0±3-2 with no lysis in the group treated rectally. The areas of lysis in the treated animals were significantly less (p<0.0001) than in the control group (160-0±12-8).

These results indicate that collagenolysis is inhibited by proteinase inhibitors and raises the possibility of using a protein (Trasylol) to reduce the risk of dehiscence of colonic anastomosis.

WP16
Alpha gliadin sensitive suppression in coeliac disease
CLJONA O'FARREL, U MCKEEVER, C FEIGHERY, C A WHELAN, AND D G WEIR (Departments of Immunology and Clinical Medicine, Trinity College, Dublin, and St. James's Hospital, Dublin, Ireland) It has been proposed that an immunoregulatory abnormality is responsible for the depressed cellular immunity in sarcoidosis, Crohn's disease, and coeliac disease and thus may be involved in their pathogenesis. It has been shown that the peripheral blood mononuclear cells (PBMCs) of Crohn's and sarcoidosis patients show increased suppressive ability when compared with normal individuals. In this study, the generation of suppression was examined in 26 untreated and 17 treated coeliac patients using a functional assay. A significantly increased level of suppression was found in both groups of coeliacs when compared with the control group.

Alpha gliadin sensitised PBMCs have been demonstrated in treated and untreated coeliac patients. The hypothesis that these cells were involved in the immunoregulatory abnormality described above was examined by testing the ability of alpha gliadin to generate suppression. Alpha gliadin activated cells from treated and untreated coeliacs demonstrated a highly significant ability to suppress Con A stimulated autologous cells. Alpha gliadin did not generate suppression in three Crohn's disease patients. Beta lactoglobulin and casein, which were also tested, showed no significant difference between the level of suppression in treated or untreated coeliac patients when compared with controls.

It is possible that alpha gliadin suppressor cells have developed to dampen the cellular and humoral response to wheat protein. Alternatively, perhaps sensitised helper cells have been immobilised in the gut in order to augment the reaction to alpha gliadin, thus depleting the peripheral blood of specific helper cells.

WP17
Effects of oral vs subcutaneous EGF on age-induced changes in rat gut epithelium
A F WREN, S R CROSBY, AND J B ELDER (Department of Surgery, Manchester University Medical School, Manchester) Seventy per cent of all fatal British cancers arise from the epithelia of the digestive tract, skin, and secretory organs. As the incidence of gastric and colonic adenocarcinoma increases with age, we have investigated the maturation-induced changes in DNA and protein content of rat gut epithelial cells. The effects of the mitogen EGF have also been examined. Male albino rats of either 2 months or 9+ months of age were randomly allocated into four groups and given saline or EGF (10 µg/kg) by gavage or subcutaneous injection six times over 48 hours. They were killed 16 hours after final injection and epithelial cells from discrete areas of the gastrointestinal tract harvested. The cell protein and DNA content were measured using the Lowry and ethidium bromide techniques respectively. There was a significant decrease in both DNA and protein content of cells from the small intestine (30% and 24% respectively) and large intestine (45% and 34% respectively) of mature rats. Subcutaneous EGF reversed all these maturation-induced changes. In contrast, oral EGF reversed only the changes occurring in mature colonic epithelial cells. In addition, oral EGF significantly increased the protein content (from 0.512 to 0.766 mg/106 cells) and DNA content (from 8.42 to 13.3 µg/106 cells) of mature gastric epithelial cells. It is possible that a maturation-induced fall in DNA and protein synthesis may result in smaller epithelial cells and that EGF can reverse this. EGF may also have a direct effect upon the gastric epithelium after oral administration.

WP18
Protein composition of ascitic fluid
G E GRIFFIN AND P KNOX (Departments of Medicine II and Biochemistry, St George's Hospital Medical School, London) Ascitic fluid and plasma were collected simultaneously from patients (n=16) with cirrhosis, nephrotic syndrome, abdominal malignancy, and tuberculous ascites. The protein composition of each ascitic fluid and plasma were compared using gel filtration chromatography. Results are expressed in terms of the level of protein in ascitic fluid compared with the level of protein in homologous plasma (Ca/Cp). This ratio for total protein is variable (0-12 to 0-78). When the ratio is calculated for proteins of differing molecular weights, however, two groups of ascitic fluid become apparent irrespective of total protein concentration. In one group the ratio is the same for all proteins. In the second group Ca/Cp varies inversely with molecular weight – that is, in comparison with plasma, proteins with lower molecular weight are more abundant in ascites.

Ascites results from an imbalance in the formation and removal of interstitial fluids formed within the peritoneal cavity. From
current knowledge of the protein composition of lymph from liver and other abdominal organs we suggest that the pathophysiology of the two groups of organs we suggest cannot be deduced from simple chromatographic analysis.

WP19
Aqueous solubilisation of triglyceride and diglyceride in pancreatic lipase deficiency

D Fine, P Zentler-Munro, J C Batten, and T C Northfield (Department of Medicine, St George's Hospital Medical School and Brompton Hospital, London) Pancreatic lipolysis is said to be a necessary prerequisite for aqueous solubilisation of lipid. This assumption is based on the finding that jejunal chyme from healthy subjects contains fatty acid and mono- and diglyceride, but virtually no triglyceride or diglyceride. No similar studies have been reported in pancreatic steatorrhoea. We have therefore studied eight patients with steatorrhoea due to adult cystic fibrosis, and eight healthy controls. Jejunal samples obtained after a Lundh meal were ultracentrifuged overnight to separate the aqueous phase. Total lipids and fatty acids were measured by titration with TEBAH with and without saponification. Glyceride classes were separated on thin layer chromatography and quantified by a hydroxamate-perchlorate method. Aqueous solubilisation of lipid was not markedly reduced in cystic fibrosis; mean fatty acid and non-fatty acid lipid (mmol/l) in aqueous phase were 3.4 and 5.8 respectively, compared with 7.2 and 6.5 in controls (NS). In preliminary studies, cystic fibrosis aqueous phase showed no detectable glyceride in low pH samples (<5), but 1.0 to 1.5 mmol/l glyceride at high pH (>6), of which 10% was mono-glyceride, 55% diglyceride, and 35% triglyceride. This pattern is consistent with lingual lipolysis; pancreatic lipolysis normally proceeds to monoglyceride formation, and there was no detectable pancreatic lipase. We conclude that in pancreatic lipase deficiency lingual lipolysis probably occurs; that diglyceride and triglyceride can enter the aqueous phase; and that pancreatic lipolysis is not a necessary prerequisite for aqueous solubilisation of fat.

WP20
FMRF-NH2-immunoreactive peptide in gut and pituitary of man and mammals

A All-Rachedi, G L Ferri, I Vardnell, J Yates, S van Noorden, L P C Schot, S R Bloom, and J M Polak (Departments of Histochemistry and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) The molluscan cardio-excitatory peptide FMRF-NH2 has recently been reported in endocrine cells of the gut and pancreas of several mammals. The identity of the immunoreactive cells has not yet been clearly defined. By immunocytochemistry, we demonstrated numerous FMRF-NH2 immunoreactive cells in the upper gut and pancreas of man, pig, cat, and guinea-pig. All immunostaining was abolished by preincubation with FMRF-NH2 at 1 nmol/ml while a range of other peptides (including gastrin, CCK, met-enkephalin, PP hexapeptide, ACTH) had a partial effect at 10 nmol/ml. The identity of the cells was established by comparing serially stained 2 μm sections. The FMRF-NH2 immunoreactive cells were characterised as G cells in duodenal and antral mucosa and PP cells in pancreas. By immunoelectron-microscopy, the FMRF-NH2 immunoreactiviety was localised to the small electron dense granules in G cells. Three gastrinomas and one PPoma were also investigated and found to contain numerous FMRF-NH2 immunoreactive cells. Both G- and PP- cells have been repeatedly reported to contain several ACTH-related peptides. We therefore studied the adrenohypophysis (man, ox, dog, pig, guinea-pig) and found FMRF-NH2 immunoreactivity to be localised in corticotrophs. In seven ectopic ACTH-producing tumours numerous FMRF-NH2 immunoreactive cells were found. Our findings demonstrate that a peptide similar to FMRF-NH2 is present in mammals including man. It is of interest that it is localised in cells producing ACTH or ACTH-related peptides.

WP21
Intestinal permeability to probe molecules

I Hamilton, J Rothwell, D A Archer, and A R Axon (Gastroenterology Unit, General Infirmary, Leeds and Department of Organic Chemistry, University of Leeds, Leeds) The passive permeability of the small intestine has been studied using a series of carbohydrate probe molecules in an animal model. The 10 molecules used had a molecular volume between 130×103 and 850×103 nm3, and none is transported by active mechanisms. An aqueous solution of each molecule is injected into a ligated loop of rat small bowel in vivo, the bladder is cannulated, and urine collected. The urinary recovery of each of the probe molecules after intravenous injection was similar, and urinary recovery therefore reflected the absorption of the probe molecule from the intestine. Molecular dimensions were calculated by a computer programme using x-ray crystallographic data.

Urinary recovery of the probe molecules was related to molecular volume but not to molecular radius or cross-sectional area. It was not possible to define a relationship between recovery and molecular volume for the entire series but molecules were divided into two distinct populations. Those with a molecular volume greater than 250×103 nm3 were absorbed less completely than those with a smaller volume; there was only a slight change in absorption with increasing molecular volume for the large molecules, while a marked reduction in absorption of the smaller molecules occurred with even very minor increases in volume.

The results demonstrate that the absorption of hydrophilic molecules with a volume in excess of 250×103 nm3 differs qualitatively and quantitatively from that of smaller molecules supporting the hypothesis that the passage of water soluble molecules across the intestinal mucosa depends on 'aqueous pores' which are of limiting size. An alternative route exists for molecules excluded from the pores because of their large volume.

WP22
Hepatic and skeletal distribution of 65Zn in cirrhosis

R W Crofton, S Gvozdanovic, D Gvozdanovic, P J Aggett, N A G Mowat, and P W Brunst (Departments of Medicine, Physiology and Biochemical Physics and Bio-Engineering, University of Aberdeen, Aberdeen) We have investigated five healthy volunteers (HV) and six patients with hepatic cirrhosis (HC). Subjects were first injected with 18-5 kBq + 0.25 mg elemental Zn; two months...
later they were given an oral dose of 92-5 kBq 65Zn incorporated into a standard meal. An ultra-high sensitivity imaging whole body counter was used to determine absorption, distribution and retention of 65Zn.

65Zn absorption in the cirrhotic patients was no different from that in the healthy volunteers (HC 33.0±12.3%; HV 31.6±1.2%). Whole body retention half-life after intravenous injection in these patients was significantly prolonged (HC 299.8±74.8 days; HV 219.0±21.8 days, p<0.05).

After intravenous injection of 65Zn there was no difference in liver uptake (HC 18.6±7.7%; HV 23.5±6.6%). After oral administration, however, there was a significant difference in uptake (HC 6.5±2.5%; HV 20.7±6.4%, p<0.05). The turnover of 65Zn in the liver can be accurately described by a two-compartment kinetics model. After intravenous injection there was the same proportion of 65Zn in the first compartment in the two groups (HC 8.8±7.7%; HV 7.1±3.3%); after ingestion there was a significant difference (HC 2.9±1.3%; HV 17.3±8.5%, p<0.05). A ratio of counts over the sacroiliac and liver region was used to quantify the transfer of 65Zn from liver to bone, which was significantly increased in cirrhosis (HC 1.33±0.60; HV 0.51±0.05, p<0.05).

Abnormal Zn metabolism is well recognised in cirrhosis. This study shows increased skeletal depositions as well as impaired hepatic uptake and retention of Zn in cirrhosis.

WP23 Adhesins in enteroinvasive strains of Escherichia coli

S KNUTION, D C A CANDY, D R LLOYD, P H WILLIAMS, AND A S MCNEISH (Institute of Child Health, University of Birmingham, Department of Genetics, University of Leicester, Leicester) Enteroinvasive strains of Escherichia coli (EIEC) produce a dysentery-like illness. Little is known about the mechanisms of mucosal attachment and epithelial cell penetration in these strains. EIEC strains 444-3 and 469-3 isolated from children with dysentery-like diarrhoea cause a mannose-resistant haemagglutination (MRHA) of human erythrocytes, adhere strongly to HEP-2 and HeLa cells but only weakly to adult human enterocytes. The adhesins have been isolated and partially purified from both strains. They appear to be proteins with subunit molecular weights of ~14,500 (444-3) and ~14,000 (469-3), show haemagglutination activity, and inhibit the adhesion of 444-3 and 469-3 to HeLa and HEP-2 cells. Mutants of 444-3 and 469-3 which lack the adhesins also lack haemagglutination activity and do not adhere to the HeLa or HEP-2 cells. Electron microscopy has revealed that the adhesins are not fimbrial antigens but are associated with the bacterial cell wall, as close apposition between cell membrane and bacterial cell wall is seen when these strains agglutinate human erythrocytes or bind to HeLa cells; adhesion to HeLa cells is predominantly to cell surface microvilli. Invasion of HeLa cells by 444-3 and 469-3 has been demonstrated by killing surface-associated bacteria with antibiotics and recovering 'internalised' bacteria from disrupted cells. The extent of invasion was ~1 bacterium/cell.

In conclusion, we have identified adhesins in two EIEC strains and demonstrated invasiveness in an in vitro system. Our observations also suggest that the formation of specific molecular contact between bacterium and cell plasma membrane is an important primary event in the process of bacterial invasion.

WP24 Hepatic, mesenteric, and splenic blood flow after digestion

B H WALMSLEY, J S FLEMING, AND S J KARRAN (University Surgical Unit and Department of Nuclear Medicine, Southampton General Hospital, Southampton) Most of our knowledge of the blood flow to abdominal organs has been derived from animal experimentation because of the invasive nature of the methods used. We have developed a non-invasive technique in the rat, which was used in the present study to determine hepatic, mesenteric, and splenic blood flow after digestion in man.

Twelve healthy volunteers underwent dynamic abdominal imaging after a bolus injection of 99mTc sulphur colloid, which is extracted by the R–E system. Initial studies were performed after a 12 hour fast and a second study after a standardised meal of 1800 kcal. Computer analysis of the stored camera images enabled effective blood flow to the various organs to be calculated.

Total hepatic blood flow rose from a mean of 1271±88.7 (SEM) ml/min to 1632±107 ml/min after the meal (p<0.01). Total mesenteric flow rose from 674±61.5 ml/min to 1280±95 ml/min (p<0.001). Splenic arterial flow fell from 257±16 ml/min to 187±16 ml/min (p<0.01). Mean hepatic arterial flow also fell from 577±40 ml/min to 352±28 ml/min (p<0.01). Pulse rate and blood pressure in the individuals at each imaging session showed no significant change.

The reduction in hepatic and splenic arterial flow described in this study lends support to the hypothesis that the increase in mesenteric blood flow brought about by digestion is due to a redistribution of blood rather than an increase in cardiac output.

WP25 Problematical boundary conditions in unstirred layer modelling

M L LUCAS AND J C TAYLOR (Institute of Physiology and Institute of Natural Philosophy, Glasgow University, Glasgow) Calculations of unstirred layer (UWL) thickness δ depend on a solution of the diffusion equation (DE). The solution usually quoted is based on the unlikely boundary condition that the membrane is impermeable to solute. In fact, only if the membrane is highly permeable is the rate of transport across the UWL determined by the latter's characteristics. Thus the usual solution corresponds to an unphysiological membrane.

A more reasonable procedure is to solve the DE with varying degrees of mucosal permeability at the UWL: membrane interface. This was done by using numerical methods to solve the fundamental equation dC/dr = D.d2C/dr2 with the boundary condition, flux through membrane = k(C1 – C2) which is non-zero, unlike the currently-used solution. Here C1 is the interfacial solute concentration, C2 is an arbitrarily low concentration across the membrane. Substitution of appropriate values of k for membrane permeability demonstrated unexpectedly that the half steady state concentration at the UWL: membrane interface was reached earlier than the simple formula t(1/2) = 0.38 8/D allows for. This simplest case solution is often used to calculate δ. With moderate to high membrane permeability, the proportionality factor can change from 0.38 to 0.18 and values as low as 0.10. The practical implications are that the simple half-time formula may be an inaccurate approximation, especially if a permeant solute such as NaCl is used to...
induce diffusion potentials from which \( \delta \) is estimated. One likelihood is that altered mucosal permeability may be erroneously interpreted as changes in UWL thickness in disease states.

**WP26**

Sites of production and inactivation of prostaglandin E\(_2\) in the rat small intestine: implications for the role of prostaglandins in the gut

G S Smith, G Warhurst, and L A Turnberg (Department of Medicine, Hope Hospital, Salford) Prostaglandins (PGs) can provoke secretion in the small intestine and may play an important role in modulating electrolyte and water transport in health and diarrhoeal disease. Endogenous PG levels will depend upon their relative rates of synthesis and degradation and the distribution of these activities in the intestinal wall will be important in determining their effects. We have therefore investigated these further in rat small intestine. Epithelial cells were separated from the subepithelium by vibration in EDTA buffer and the synthetic and degradative capacity of these fractions determined, by RIA for PGE\(_2\) and radiochemical detection of the PGE\(_2\) metabolites formed respectively. Synthesis was located almost exclusively in the subepithelial fraction (subepithelium 76.5 ± 15.6; epithelium 1.45 ± 0.47 p.mol.min\(^{-1}\) (mg protein\(^{-1}\)), whereas degradation was found predominantly in the epithelial cell fraction (subepithelium 36.3 ± 7.9; epithelium 274 ± 22.3 p.mol.min\(^{-1}\) (mg protein\(^{-1}\)); n=6). Separation of the epithelial cells into a villous to crypt gradient demonstrated that the capacity to degrade PGE\(_2\) decreased from villous to crypt, whereas the responsiveness of epithelial adenylate cyclase to exogenous PGE\(_2\) increased and was maximal in the crypts. Subepithelial adenylate cyclase activity was poorly stimulated by PGE\(_2\).

These data support the hypothesis that PGE\(_2\) is synthesised in the subepithelial tissues and degraded in the epithelium where it activates secretion. On the basis of adenylate cyclase responsiveness secretion is likely to be maximally located in the crypt epithelium.

**WP27**

Influence of a new selective 5-HT\(_2\) receptor antagonist (ketanserin) on jejunal PGE\(_2\) release and ion secretion due to malignant carcinoid syndrome

S Antonsen, M G J Hansen, K Bukhave, and J Rask-Madsen (Department of Medical Gastroenterology, Odense University Hospital, and Department of Medicine C, Herlev Hospital, University of Copenhagen, Denmark) Recent work has implicated prostaglandins (PGs) released by excessive 5-hydroxytryptamine (5-HT) in the pathophysiology of carcinoid syndrome. A PG mediated 5-HT effect in carcinoid syndrome has been questioned because anti-inflammatory agents as well as classical 5-HT antagonists appear ineffective in ameliorating diarrhoea and flushing. Two distinct 5-HT receptors exist, but only binding to the 5-HT\(_2\) receptor correlates with both in vitro and in vivo effects of 5-HT. This has prompted us to investigate whether the new selective 5-HT\(_2\) receptor antagonist, ketanserin, would affect jejunal release of PGE\(_2\) and – like somatostatin – inhibit intestinal ion secretion, diarrhoea, and flushing in carcinoid syndrome.

In a 68 year old female with metastasising midgut carcinoid oral treatment with ketanserin for eight days (20 mg tid) reduced immunoreactive PGE\(_2\) levels in jejunal fluids from 1255 to 385 pg/ml (5–205 pg/ml–99% confidence limits), decreased stool volumes from 0.75 to 0.39/day \( \langle p \rangle 0.02 \), and relieved flushing attacks. Jejunal perfusion studies before medication revealed net secretion of fluid, Na\(^+\), Cl\(^-\), and K\(^+\). Ketanserin infused intravenously for 60 minutes (10 mg + 2 mg/h) decreased net secretion of fluid, Na\(^+\), K\(^+\), and Cl\(^-\) and increased lumen to plasma fluxes of Cl\(^-\) (\( p \rangle 0.05 \)). Additional infusion of somatostatin the following 60 minutes (8 \( \mu \)g/kg/h) reversed net secretion to absorption (\( p \rangle 0.001 \)). Spontaneous secretion of Na\(^+\) and Cl\(^-\) occurred mainly as a consequence of increased plasma to lumen fluxes, which decreased (\( p \rangle 0.001 \)) in response to combined ketanserin/somatostatin infusion. These results suggest that ketanserin and somatostatin inhibited a PG-mediated 5-HT sensitive secretory component of fluid and ion movement in the small intestine of the patient with carcinoid syndrome.

**WP28**

Cholesterol esterase activity of human intestinal mucosa: properties of the enzyme and effect of different bile acids

F Carubbi, M Ponz de Leon, P di Donato, and N Carulli (Istituto di Clinica Medica II, Università di Modena, Modena, Italy) It has been suggested that cholesterol absorption is increased by cholic acid feeding, whereas it tends to decrease after administration of dihydroxy bile acids. In this context it has been shown, in rats, that cholic acid and its conjugates stimulate the activity of cholesterol esterase – an enzyme which appears to be involved in the capacity of the rat intestine – and in this way may promote cholesterol absorption; in contrast, dihydroxy bile acids are much less effective. The aim of this study was to determine some general properties of the human cholesterol esterase and, in particular, to investigate the effect of different bile acids on cholesterol esterase activity. Eighteen samples (2–5 cm) of normal terminal ileum were obtained at surgery for total or hemicolectomy. The mucosa was scraped off and homogenised in phosphate buffer containing the investigated bile acid. Cholesterol (23.2 \( \mu \)mol + 1 \( \mu \)Ci \( ^{3} \)C-cholesterol) and oleic acid (139 \( \mu \)mol) were added and the mixture (total volume 6 ml) was incubated at 37°C for one to 24 hours. Experiments were carried out at 0.4, 0.1, 1.0, and 2.0 \( \mu \)mol/l of bile acids. Cholesterol esters were separated by TLC and the enzymatic activity expressed as nmol of esters formed/h/g of mucosa.

The time-activity relationship was linear for two hours; by increasing the amount of proteins (1.5–3.6 ml of homogenate) a linear increase of esterification was observed. Subcellular distribution (by ultracentrifugation) of cholesterol esterase activity was a follows: 78%±12% in the supernatant, 20%±2% in the microsomes, and trace in the nuclei and mitochondria. Optimal pH ranged between 5.4 and 6.2. In absence of bile acids cholesterol esterase activity was 188±25 nmol/h/g. Bile acids, either individually or in a mixture of physiological proportion, did not change cholesterol esterase activity when added at 0.1 and 1.0 mmol/l (range of activity 154–206 nmol/h/g), whereas the activity was significantly \( \langle p \rangle 0.01 \) reduced (range of activity 57–106) when bile acids were added at 20 mmol/l.

We conclude that cholesterol esterase activity is detectable in human ileal mucosa and shows similarities with the rat enzyme. At variance with this species, however, human cholesterol esterase does not appear to be affected by bile acids and, indeed, high concentrations may actually inhibit cholesterol esterase activity.
WP29
Changes in the structure of the human surface gastric mucus gel in disease
R. Ward, J. P. Pearson, C. W. Venables, and F. Younan (Department of Physiological Sciences, Department of Surgery, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne) The mucus gel covering the gastric mucosal surface consists of a high molecular weight glycoprotein which, on proteolysis, results in a lower molecular weight form lacking the viscous and gel-forming properties of the native glycoprotein. We have shown that gastric mucus gel from mucosa resected for gastric ulcer or duodenal ulcer contained higher proportions of lower molecular weight glycoprotein than that from normal mucosa obtained by pancreateoduodenectomy for periampullary carcinoma.

In the present studies surface mucus from resected antral mucosa of patients with gastric carcinoma contained significantly more lower molecular weight glycoprotein (76.8±2.4%) compared with patients with gastric ulcer (65.1±2.8%), duodenal ulcer (50.2±3.3%), or normal mucosa (33.4±5.1%). The results were unaffected by the use of isolation buffer at pH 2.7 or pH 7.0 or addition of a cocktail of proteolytic enzyme inhibitors; evidence that the results reflect the state of the mucus in vivo rather than degradation during the isolation procedure.

Our results show there is a higher proportion of lower molecular weight glycoprotein in mucus gel from patients with gastric pathology than in normal stomachs, implying weakening of the gastric mucus barrier.

P3
Nature of the bleeding point in massively bleeding gastric ulcers
C. P. Swain, S. G. Bown, P. R. Salmon, T. C. Northfield, J. S. Kirkham, and J. O'Sullivan (The Norman Tanner Gastroenterology Unit and Department of Histopathology, St James's Hospital, and the Department of Gastroenterology, University College Hospital, London) This study examines endoscopic findings to postoperative angiographic and histological observations on the nature of the bleeding point when gastric ulcers bled massively. Emergency endoscopy in 580 patients admitted for upper gastrointestinal haemorrhage revealed peptic ulcers in 281; full examination of the ulcer was possible in 231. Visible vessels were identified in 110, other stigmata of recent haemorrhage in 47, and no stigmata of recent haemorrhage in 74. Ninety-four patients with stigmata of recent haemorrhage, randomly allocated to no endoscopic treatment, were observed for evidence of rebleeding. Thirty-eight of 68 patients with visible vessels rebled (56%) compared with two of 26 with other stigmata of recent haemorrhage (8%) (p<0.001). Nineteen patients in whom a visible vessel was identified endoscopically were subsequently submitted to emergency surgery for rebleeding and the resected specimen was available for study. In 18 of these (95%) the vessel identified endoscopically was found in the specimen. The vessel protruded above the ulcer crater in four, and clot in continuity with the breach in the vessel wall protruded in a further 12. The bleeding artery (mean external diameter 0.6 mm in the fixed specimen - range 0.3-1.5 mm) was submucosal in 11 and serosal in seven. Angiography, when technically possible, showed the breech...
artery to cross the ulcer in all. The dominant pathological changes at the bleeding point were arteritis with fibrinoid necrosis (14), loose fibrous intimal thickening (10), and recanalised thrombus (four). The ulcer penetrated to serosa in 10. These observations are of relevance in planning endoscopic therapy. They also validate endoscopic identification of a visible vessel and confirm that such identification is helpful in predicting recurrent haemorrhage.

P4 Soya-induced pancreatic hypertrophy and rise of circulating cholecystokinin

T E ADRIAN, C PASQUALI, F PESCOSTA, A J BACARESE-HAMILTON, AND S R BLOOM (Department of Medicine, Royal Postgraduate Medical School, London) Soybean flour which is used increasingly for dietary protein supplementation in man contains a heat labile trypsin inhibitor which causes pancreatic hypertrophy in experimental animals. This increase in pancreatic growth can be prevented by proximal intestinal resection, suggesting that a gut hormone mediates the effect. Thirty male Wistar rats were fed on raw soybean flour for 21 days and 30 controls were pair-fed with flour in which the enzyme inhibitor had been heat-inactivated (130°C, 30 min). Plasma CCK concentrations were measured using a subtraction system with two antibodies, one raised to sulphated CCK-8 measuring all gastrins and CCKs and the other specific for the gastrins. Both assays can detect changes of 0-2 pmol/litre with 95% confidence. After 21 days the pancreatic weight of the group receiving active trypsin inhibitor had increased by 76% compared with controls (2-71±0-08 g vs 1-53±0-04 g, p<0-005). Similarly, plasma CCK levels were grossly raised in this group (24-5±3-1 pmol/l vs 8-2±0-8 pmol/l, p<0-001). There was also a small increase in plasma gastrin concentrations from 31±3 pmol/l in controls to 46±4 with enzyme inhibitor (p<0-005).

Thus pancreatic hypertrophy resulting from a dietary protease inhibitor is accompanied by an increase in CCK and also gastrin. In the light of the current epidemic of pancreatic cancer in the western world (and also soya consumption) the study of factors which cause hypertrophy of this organ is of great importance.

P5 Periampullary diverticula and common duct calculi: a combined transhepatic and endoscopic technique for difficult cases

A R W HATFIELD, R S MURRAY, AND J E LENNARD-JONES (Academic Unit of Gastroenterology and Department of Radiology, The London Hospital, Whitechapel, London) The relationship between periampullary diverticula and common bile calculi is not fully understood. The distal route of the bile duct around the diverticulum may encourage stasis and hence stone formation. The presence of the diverticulum and site of the papilla may make endoscopic sphincterotomy difficult if not impossible.

In a series of 263 consecutive patients without gall stones undergoing ERCP (age range 20-90 years, mean 59 years) periampullary diverticula were found in 20 (8%). In 119 consecutive patients with common bile duct calculi (age range 32-92 years, mean 67 years), however, diverticula were present in 42 (35%) (p<0-001). If older patients (>60 years) without gall stones were examined, diverticula were seen in only 10 of 82 patients (12%) (p<0-001).

Endoscopic sphincterotomy was attempted in 68 patients. Diverticula were present in 29 patients, with the papilla on the edge in 21 and inside the diverticulum in eight. In three patients sphincterotomy was impossible as the papilla was inside the diverticulum. Using a transhepatic catheter and guide-wire, the papilla can be brought towards the duodenal lumen. The orifice can even be dilated with a Grundzig balloon catheter. It is then easy to follow the direction of the guide wire and perform a sphincterotomy.

There appears to be a close association between diverticula and common bile duct calculi. This combined approach facilitates endoscopic sphincterotomy even when the papilla is hidden inside a diverticulum.

P6 Selective and non-selective B blockade in the reduction of portal hypertension

D WESTABY, A E S GIMSON, D BIHARI, I R CROSSLEY, AND R WILLIAMS (The Liver Unit, King's College Hospital and Medical School, London) It has recently been suggested that the reduction in portal pressure after propranolol administration is due to a fall in hepatic blood flow resulting from the drug-induced reduction in cardiac output. To test this hypothesis we have studied the effect of a selective (metoprolol) and a non-selective B blocker (propranolol) on cardiac output (CO; thermodilution technique), estimated hepatic blood flow (EHBF; ICG clearance), and portal pressure (wedged-free hepatic venous pressure) in 18 patients with cirrhosis and recent variceal bleeding. Patients were randomly allocated to receive a single intravenous dose of either propranolol or metoprolol to reduce pulse rate or cardiac output by 15%. There was a comparable reduction in pulse rate and CO in both groups. Portal pressure fell significantly in both groups (p<0-005) but was more marked with propranolol (mean fall 6-8 mmHg) than metoprolol (mean fall 3-6 mmHg). In the propranolol group there was a reduction in EHB, of 20-4% (pre 1-4±SD 0-15 l/min; post 1-13±SD 0-16 l/min, p<0-005), while there was no change with metoprolol (pre 1-15±SD 0-21 l/min; post 1-17±SD 0-23 l/min). In neither group was there any correlation between fall in cardiac output and change in portal pressure or hepatic blood flow. There was a significant relationship, however, between the decrease in EHB and the fall in portal pressure with propranolol (r=0-80, p<0-01).

Thus, the fall in portal pressure after B blockade cannot be entirely explained by a fall in cardiac output or EHB. The greater fall in portal pressure and the significant changes in EHB seen with propranolol suggest that B2 receptor blockade in the splanchic bed may contribute to the reduction in portal pressure.

P7 Alpha gliadin and ELISA (enzyme-linked immunosorbent assay): a serological test for coeliac disease.

CLIONA O'FARRELLY, J KELLY, B BRADLEY, A THOMPSON, G MACDONALD, W HEEKENS, AND D G WEIR (Departments of Immunology and Clinical Medicine, Trinity College, Dublin, and St James's Hospital, Dublin) The ELISA system was adapted to measure antibody levels to wheat protein with a view to developing a serological test for coeliac disease. Using this assay, there was no significant difference between the ELISA indices (EI) of 26 untreated coeliac patients and 26 controls when the following antigens were used: digested gluten, gliadin, β and α gliadins, casein, or β lactoglobulin. In contrast,
using α gliadin, significantly raised ELIs were found in coeliac disease but not in the normal control group nor in 13 patients with Crohn’s disease (p<0.001 in both cases). These results indicated that αGA levels are specifically raised in coeliac disease.

To test the validity of this assay for the diagnosis of coeliac disease, αGA levels were estimated in 75 patients being investigated for the disorder. The levels were raised in 31/35 patients whose jejunal biopsies were diagnostic of coeliac disease, whereas in 40 individuals with normal jejunal mucosa, four had raised αGA levels (p<0.001).

Eleven patients were started on a gluten-free diet and serial serum samples were obtained to determine the effect of the diet on the αGA levels. A further jejunal biopsy was obtained six months after starting treatment. The jejunal biopsies of eight patients were consistent with that of treated coeliac disease and in 7/8 cases the αGA levels decreased with time. In three patients, the jejunal biopsy was consistent with untreated coeliac disease indicating non-dietary compliance; in each case the αGA levels remained raised.

The results of this study indicate that estimation of αGA levels by ELISA is a useful screening test for coeliac disease and may be used to monitor compliance with gluten-free diet.

Metabolic bone disease was present in 30 patients (73%), consisting of osteomalacia and secondary hyperparathyroidism. Patients with bone disease were significantly older than those without (38.5±10.9 years; mean ± SD, vs 29.2±6.9, p<0.02), but did not differ significantly with respect to type of operation, time since operation, or post-operative weight loss. Plasma calcium and alkaline phosphatase did not differ significantly between the two groups, but the plasma phosphate was significantly lower in patients with bone disease (3.34±0.6 mmol/l vs 3.86±0.5; p<0.02). Plasma 25(OH)D levels were normal in all 41 patients.

We conclude that metabolic bone disease is common after either partial or total biliopancreatic bypass and is associated with normal plasma 25(OH)D levels. The pathogenesis of the bone disease is unclear, but simple vitamin D deficiency appears unlikely to be important.

T3
Dark red bleeding as a marker comparable with faecal occult blood testing in screening for large bowel neoplasms

R J Nicholls, A J Silman, P Mitchell, F Macrae, R J Lees, C J Bartram, and M Simmons (St Mark’s Hospital, London, and The London Hospital, London) The prevalence of large bowel symptoms and their association with large bowel neoplasms were investigated among employees of two industrial organisations. Results were compared with faecal occult blood testing (Haemoccult, Eaton Laboratories).

Symptom questionnaires and Haemoccult kits were returned by 916 out of 1805 employees (>40 years) (compliance 50.7%). Twenty-eight (3.1%) were Haemoccult positive and 114 (12.4%) had one or more symptoms including bleeding in 108 (11.8%). All positives (129 persons) were examined by flexible endoscopy and barium enema and polyps were removed for histological examination. No cancer was found but seven patients with an adenoma >10 mm in diameter were discovered. Haemoccult was positive in six but all seven had at least one symptom: dark bleeding (four), bright bleeding (two), diarrhoea (one). Predictive values for an adenoma >10 mm for Haemoccult (21.4%), dark bleeding (16.0%), and diarrhoea (16.6%) were not significantly different, but these values were greater than those for bright bleeding (2%), mucus (0%), and constipation (0%) (p<0.05). The predictive value of a positive Haemoccult test plus at least one symptom increased significantly to 46% (p<0.05).
Faecal occult blood testing in screening may not be identifying 'asymptomatic' cases as often as has been previously presumed. A symptom questionnaire may reduce the false positive rate of Haemocult and dark bleeding might be a useful marker for neoplasms in screening.

T4 When can antibiotics be used safely in patients with active or recently treated Clostridium difficile colitis?

R P BOLTON AND M S LOSOWSKY (University Department of Medicine, St James's Hospital, Leeds) The need for continued antibiotic therapy in some patients with antibiotic-induced Clostridium difficile colitis poses a real clinical problem and the effect of concurrent or subsequent antibiotic therapy given for other conditions on the course of the disease has not been established. Of 11 patients with C. difficile colitis, six received additional antibiotics during therapy; all responded clinically with clearance of organism and toxin and none relapsed. Antibiotics were subsequently used on 20 occasions in nine patients after therapy with C. difficile had ceased. C. difficile colitis recurred in two patients; both had responded well to vancomycin with clearance of faecal toxin, but both had residual faecal organisms. Seven patients remained well during 18 subsequent episodes of antibiotic usage; all had cleared C. difficile after initial therapy and none reacquired the organism or faecal toxin. Patients receiving specific antimicrobial therapy for C. difficile colitis are unlikely to be affected by antibiotics given for intercurrent infection, and prophylaxis during subsequent antibiotic therapy is not indicated in those patients who have cleared C. difficile from their stool. Relapse may occur during subsequent antibiotic therapy in those patients with persistent faecal C. difficile despite symptomatic recovery, and prophylaxis is probably indicated in this group of patients.

T5 Does failure of bisacodyl-induced colonic peristalsis indicate intrinsic nerve damage?

D M PRESTON AND J E LENNARD-JONES (St Mark's Hospital, London) Previous work has suggested that patients with constipation show excessive colonic segmenting activity. Patients complaining of constipation can be divided into two groups. Some (presumed irritable bowel syndrome, IBS) have normal whole gut transit rate and pain is prominent; others (termed slow-transit constipation, STC) have a prolonged transit rate and decreased bowel frequency is the major symptom. The motility of the pelvic colon has been studied in 28 patients over one hour under resting conditions after a 12 hour fast. The mean motility index for each group was: controls 1803±297 SEM, IBS 11,934±3066, STC 397±91. This finding suggests that hypersegmentation occurs only in some patients complaining of constipation; others tend to have an inert colon.

Eighteen patients with STC were studied after the introduction of a surface acting laxative at 25 cm from the anus. In 11 patients a normal response was seen with peristaltic waves passing caudally. The motility index in this group over 30 minutes rose from 201±54 to 7201±1874 (p<0.001). In seven patients there was no response. Motility index 153±68 to 262±146 (NS). The patients who responded tended to be younger and have a shorter history. Six of seven non-responders reported being given regular laxatives before the age of 10, compared with two of 11 who responded.

The topical effect of bisacodyl may be a test of intrinsic nerve function.

T6 Elemental diets in the treatment of acute Crohn's disease: a controlled study

C A O'MORAIN, A W SEGAL, AND A J LEVI (Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex) A randomised controlled single centre study was conducted to compare the efficacy of an elemental diet (Vivonex) for one month with that of prednisolone 0-5 to 0-75 mg/kg body weight. Patients were entered into study who had acute severe documented Crohn's disease and who had received no previous specific therapy. The patients were assessed by a prearranged clinical storing system for symptoms and signs, body weight, haemoglobin, erythrocyte sedimentation rate, and serum albumin estimated at entry and weekly intervals for the duration of the trial and at three months' follow-up. Twenty-one consecutive patients were entered into the trial, aged 15-68 years; 14 males, seven females. Ten received steroids and 11 patients an elemental diet. The two groups were comparable for age, site, and activity of disease. Two patients in each group were withdrawn from the trial. Eight of the 10 steroid-treated patients and nine out of the 11 elemental diet treated group were considered to be in clinical remission at the end of the trial period. There was a significant fall in clinical score, ESR, and an increase in haemoglobin and albumin in both treatment groups at four weeks compared with base line values when analysed by one-way analysis of variance. There was no difference in these parameters between both groups. At three months one patient in each group had relapsed. The patients in the steroid treatment group were receiving prednisolone 10–15 mg/day, whereas the elemental diet group were on no specific therapy. We conclude from this study that an elemental diet is as effective as steroids in inducing a remission in acute Crohn's disease and is simple and safe to administer.

T7 Granulomatous crypt destruction: a subtle lesion of Crohn's disease?

G HOLDSWORTH, CLAIRE DU BOULAY, C L SMITH, AND P ISAACSON (Department of Medicine and Pathology, Southampton General Hospital, Southampton) We describe a lesion, which we have named granulomatous crypt destruction, which can be used to differentiate between ulcerative colitis and Crohn's disease. The lesion is characterised by a collection of macrophages, some almost epithelioid in type, and associated eosinophils, which are destroying crypts. The lesion has been found in rectal biopsy material from 14 patients with inflammatory bowel disease (seven males and seven females, age range 24-72 years). The duration of disease before recognition of this lesion ranged from six months to 12 years. All patients were previously clinically considered to have ulcerative colitis with diarrhoea, blood, and mucus. None had significant pain. Only one patient had an anal fissure and none had rectal sparing. Barium meal and follow-through was normal in all patients and barium enema showed distal changes in eight patients but was normal in six patients. Colonoscopy, with biopsies, revealed more extensive disease in all and showed two patients to have 'skip lesions' and another five to have true granulomas in biopsies from other sites.
review of histological material available showed preserved architecture, a paucity of crypt abscesses, and focal changes more in favour of Crohn's disease than ulcerative colitis.

We consider granulomatous crypt destruction to be an important finding in a subgroup of patients with Crohn's disease. Furthermore, if granulomatous crypt destruction represents a partial granulomatous response it is suggested that inflammatory bowel disease is a spectrum of disease possibly dependent on the individual's ability to form granulomas.

T8 Sulphasalazine-induced reversible male infertility in man and rat

C A O'MORAIN, P SMETHURST, AND A J LEVI (Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex) In clinical studies semen was analysed from 26 men (age 19-30 years) taking 2-4 g sulphasalazine (SASP) daily and compared with semen from 25 men (age 22-42 years) with inflammatory bowel disease not on SASP for the preceding three months. There was a significant decrease in sperm counts (31.9±6.4 vs 62.6±7.9×10^6 ml) and motility 24.2±1.6 vs 49.3±3.1) progressively migrated, and a deterioration in morphology in the treated patients. The semen quality improved three months after withdrawal. Fourteen pregnancies resulted after withdrawal (median 2.5 months). Three patients fathered children while on the drug. Serum acid phosphatase, fructose, and PGE2 were measured in 10 treated patients and showed no difference from normal levels. Gonadotrophin hormone profile was identical in eight patients while on and off SASP for three months. Male rats fed SASP had a dose dependent reversible reduction in litter size when mated (13-7 to 3-0 live foetus). Libido was unaffected. The effect was reversed within 14 days of drug withdrawal. The uteri of female rats mated with treated males showed a significant decrease in fertilised eggs at the two cell stage compared with controls (2-4 vs 12). Sulphapyridine but not 5-amino-salicylic acid nor a SASP polymer induced a similar reduction in litter size. We conclude that SASP causes a reversible infertility in man and rat. This is not related to ill health or inflammatory bowel disease. The time course, morphology, and recovery experiments suggest a quantitative effect on later stages of sperm maturation. The SP part of the SASP molecule is responsible for infertility as well as other side-effects and this should stimulate the formulation of other compounds such as SASP polymers, for use in inflammatory bowel disease.

T9 Oral 5-amino salicylic acid for the maintenance of remission in ulcerative colitis: a controlled trial

M J DEW, P J HUGHES, A D HARries, G WILLIAMS, B K EVANS, AND J RHODES (Departments of Gastroenterology, Pharmacy and Pathology, University Hospital of Wales, Cardiff) 5-amino salicylic acid (SASP) is the active constituent of sulphasalazine (SLP salazopyrine), which is released in the colon, healing and probably preventing relapse in ulcerative colitis. The effect of SASP on the colon is likely to be related to local release and a topical effect which could not be achieved after simple oral administration because of absorption by the small intestine. We have recently described a 'colonic delivery system' whereby oral preparations coated with an acrylic-based resin (Eudragit S) 120 μ in thickness are released in the colon. This double-blind randomised study compares the effectiveness of SASP coated in this way with SLP for the maintenance of remission in ulcerative colitis. Seventy-two patients (36 male and 36 female) with ulcerative colitis in remission on at least 2 g SLP/day (less than three stools per day without blood or slime for one month) were given either active SASP and placebo SLP or active SLP and placebo SASP for 16 weeks. The minimum dose of SASP was 1-2 g per day and of SLP 2 g/day. Sigmoidoscopy was performed at entry into the trial and at the time of relapse or on completion of the trial period. Sixty-seven patients completed the trial with 15 relapses, nine on SASP, and 6 on SLP (p not significant). SASP coated with Eudragit S and SLP are equally effective for prevention of relapse in ulcerative colitis.

T10 Impact of Crohn's disease in childhood

J PUNTIS, A S MCNEISH, AND R N ALLAN (Gastroenterology Units, General and Children's Hospital, Birmingham) The impact of Crohn's disease in childhood has been evaluated in a series of 67 children (M=37, F=30) whose symptoms started before 16 years of age. The mean age at onset of symptoms was 13-0 years and at diagnosis 14-5 years. The distribution of disease at diagnosis was distal ileum 37%, ileum + right colon 19%, colon alone 27%, diffuse small bowel disease 13%, other 3%. During review 21% developed diffuse small bowel disease. At presentation abdominal symptoms were nearly always present (87%) often combined with weight or height retardation (39%). Weight loss or height retardation alone was rare (6%). Retardation was usually corrected by surgical intervention and was a permanent feature in only five patients.

Cumulative recurrence rates after ileo-colonic resection were initially higher than in the adult group: at one year 7% vs 5%, five years 33% vs 20%, but similar at 10 years (54% vs 49%).

Nine patients have died, six with diffuse small bowel disease. The causes of death were disease related (three), associated disorders (three), drug induced (two), unrelated (one).

Of the 58 survivors 38 are currently fit and well with no evidence of recurrent disease, 14 have evidence of recurrent or residual disease but are symptom free, while six have asymptomatic recurrent or residual disease.

The initial high morbidity poses challenges in management, but the long-term prognosis is good in most patients.

T11 What length of terminal ileum is required for bile salt absorption?

G COOPER, B J ABEL, A G HUTCHISON, AND C MACKAY (Department of Surgery, Western Infirmary, Glasgow, and Department of Urology, Victoria Infirmary, Glasgow) The critical length of ileal resection necessary to cause malabsorption of bile salts and vitamin B12 has not been clearly defined by previous work on the subject. With regard to bile salts, however, 40 cm has been suggested.

The use of terminal ileum in urinary conduit construction results in an interesting model since a standard length, approximately 25 cm, is isolated for the technique. Bowel habit, faecal bile salt excretion, and vitamin B12 were investigated in 12 patients who had undergone this operation. Seven had developed looseness or frequency of stool. Bile salt losses were determined by gas-liquid chromatography using three-day
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The mean faecal bile salt excretion was 56.00 mmol/day and the output 6.22 mmol/day in comparison with control values of 24-97 mmol/day and 0-53 mmol/day respectively; both these differences were statistically significant (p<0.025 and p<0.001). Four patients had subnormal Schilling test results.

Terminal ileal resections of the order of 25 cm, therefore, are likely to cause abnormal faecal bile salt losses and may result in vitamin B₁₂ malabsorption. Choledochal diarrhoea, cholesterol gall-stone formation, and megaloblastic anaemia are possible consequences of using ileum to make a urinary conduit.

T12

Quantitative faecal excretion of ³¹In-labelled autologous granulocytes in assessment of disease activity in Crohn's disease

S H SAVERY-MUTTU, A M PETERS, M B PEPS, J P LAVENDER, H J HODGSON, AND V S CHADWICK (Departments of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London) Assessment of disease activity in Crohn's disease involves determination of either clinical indices – for example CDAI – or laboratory (ESR, CRP, orosomucoids) measurements. These are indirect and non-specific correlates of gut inflammation. Neutrophil granulocyte infiltration of the intestine is the characteristic histological feature of disease activity but quantitative histology of biopsies from different and sometimes inaccessible regions of the gut to assess activity is often impractical. In preliminary studies with ³¹In-labeled mixed leukocyte preparations we reported that faecal ³¹InIndium excretion after intravenous administration of labelled cells correlated with disease activity in inflammatory bowel disease. We have now developed a method of efficiently labelling pure granulocyte preparations in plasma using a discontinuous plasma density gradient technique and ³¹InTropolonate chelation. With this technique we have compared quantitative faecal granulocyte excretion with conventional parameters of disease activity in 32 studies in patients with Crohn's disease.

Results showed that faecal granulocyte excretion ranged from 1.5 to 52% of the injected dose and was significantly correlated with CDAI (r=0.731, p<0.001), ESR (r=0.676, p<0.001), and CRP (r=0.716, p<0.001). Quantitative faecal excretion of ³¹In labelled granulocytes is a reliable method of assessing disease activity in Crohn's disease, is specific for gut inflammation, and is suitable for objective assessment of disease activity in therapeutic trials.

T13–T24

LIVER/GUT IMMUNOLOGY

Platelet associated immunoglobulins in primary biliary cirrhosis (PBC)

M F BASSENDINE, J COLLINS, J STEVENSON, P SAUNDERS, AND O F W JAMES (Department of Medicine, Freeman Hospital and Department of Haematology, General Hospital, Newcastle upon Tyne) Thrombocytopenia in cirrhotic patients is classically attributed to splenic pooling, whereas in idiopathic thrombocytopenia purpura (ITP) it is related to surface bound immunoglobulin (IgG). Recently platelet associated IgG (PAIg) has been reported in patients with chronic liver disease, mainly alcoholic cirrhosis. We have now looked for PAIg in primary biliary cirrhosis, as this is an 'autoimmune' disorder, in order to assess the frequency and possible relationship of PAIg to thrombocytopenia in this condition. PAIg was estimated by a method using radio-labelled staphylococcal protein A; in our laboratory normal subjects have a mean PAIg of 0.89±0.38 (n=50), whereas in ITP 87.5% patients (n=48) have raised PAIg (>1.6). Spleen size was graded 0–3 on colloid scan by an independent observer.

Sixty-two primary biliary cirrhosis patients were studied (28 stage I–II, 34 stage III–IV). Raised PAIg was found in 25 patients (40%) of whom 18 had cirrhosis. Thrombocytopenia (<100,000) was found in nine (15%), all were cirrhotic. Whereas there was no correlation between platelet count and amount of PAIg (r=0.14) or spleen size (r=0.03) in the total group, in the nine thrombocytopenic patients all had raised PAIg (p<0.005) and eight had spleen size 2 or 3 (p<0.005). Two of these with bleeding and platelets <30,000 were treated with steroids with great benefit.

We conclude that platelet bound immunoglobulins, present in 40% patients with primary biliary cirrhosis, may contribute to thrombocytopenia, particularly in the presence of splenic enlargement. Steroid treatment may benefit such patients.

T14

Different immunoregulatory mechanisms for IgM production and B cell proliferation

K NOURI-ARIA, J NEUBERGER, AND A L W F EDDLESTON (The Liver Unit, King's College Hospital and Medical School, London) To investigate suppressor cell function in patients with primary biliary cirrhosis and its relationship to increased IgM production, the ability of unconcanavalin A (Con A) to inhibit differentiation and secretion of IgM producing cells was measured by haemolytic plaque and immunofluorimetric assays in 20 normal subjects and 23 patients with primary biliary cirrhosis. Monomeric and pentameric IgM were also determined by immunodiffusion in polyacrylamide/agarose. The median number of IgM producing cells in primary biliary cirrhosis was comparable with normal subjects (1811 and 1798/10⁶ lymphocytes, p>0.05). whereas the amount of IgM secreted into culture media was significantly greater in primary biliary cirrhosis than in normal subjects (1887 and 792 ng/10⁶ lymphocytes, p<0.01). Thus, IgM synthesis per B cell was significantly increased in primary biliary cirrhosis compared with normal levels (p<0.05). Autologous Con A activated suppressor cells inhibited IgM production significantly less than controls (% suppression = 52.1 ± 25.2 and 69.1±16.7, p<0.05), but inhibition of proliferation was comparable with normal subjects. Monomeric IgM was found in 37% of primary biliary cirrhosis sera and was related to the serum IgM level measured by nephelometry. These observations suggest that control of proliferation of B cells and secretion of immunoglobulin may be under separate immunoregulation and that in primary biliary cirrhosis suppression of proliferation of IgM producing cells is normal but control of secretion is abnormal. Whether this defect is due to an intrinsic abnormality of B cell function or a suppressor cell abnormality remains to be determined.

T15

Significance of delta agent infection in chronic hepatitis B viral infection in Great Britain

I V D WELLER, P KARAYANNIS, A S F LOK, M BAMBER, H C THOMAS, AND S SHERLOCK (Department of Medicine, Royal Free Hospital and School of Medicine, London)
Medicine (University of London) London) Delta antigen (δ) is a transmissible agent requiring hepatitis B virus (HBV) for its replication. It is prevalent in Italian HBV carriers and more common in patients with chronic liver disease. HBV carriers with current δ infection have a serum antibody (anti-δ), in high titre, detectable by radioimmunoassay. The prevalence of anti-δ in British HBV carriers is unknown. Seventy-one HBV carriers born and resident in Great Britain were studied. Fifty-nine had abnormal LFTs and 49 histologically proven chronic liver disease. Stored sera together with samples from HBsAg negative controls were coded and analysed blind for anti-δ by Dr M Rizzetto (Turin, Italy). Anti-δ was positive in nine out of 71 (13%) British HBV carriers: six were intravenous drug abusers and two were haemophiliacs. Anti-δ was negative in 30 homosexual HBV carriers. Cirrhosis was more common in patients with anti-δ and those with anti-δ positive cirrhosis were significantly younger than those with anti-δ negative cirrhosis. Anti-δ was not found in HBsAg negative blood donors (n = 100) or haemophiliacs (n = 79). Two out of 58 HBsAg negative intravenous drug abusers had anti-δ in low titre and both had anti-HBc and anti-HBs indicating recent infection with HBV and δ. In British HBV carriers δ infection is associated with intravenous drug abuse and haemophilia and perhaps a more rapid progression of chronic liver disease.

T16 T-cell cytotoxicity and circulating T-cell subsets in chronic HBV infection

M Mondelli, G J M Alexander, N Nouri-aria, A L W Eddleston, and R Williams (The Liver Unit, King's College Hospital and Medical School, Denmark Hill, London) The proportion of peripheral blood lymphocytes (PBL) reacting with the monoclonal anti-T-cell antibody OKT8 is increased in untreated patients with chronic hepatitis B virus (HBV) infection and, as this antibody reacts with a suppressor cell population, this has been interpreted as indicating altered immunoregulation in these cases. However, OKT8 also reacts with cytotoxic T cells and the possibility that these cells are responsible for the increased proportion of OKT8+ PBL in this virus-related disease has largely been ignored. We have therefore investigated the relationship between the cytotoxicity of T enriched PBL for autologous hepatocytes and the proportion of OKT8+ cells measured by indirect immunofluorescence in 13 patients with chronic HBV infection, eight of whom had HBeAg in serum. Five were on corticosteroids and one of these was also on cyclosporin. Percentage T-cell cytotoxicity was higher in HBeAg positive than HBeAg negative patients (40-1±25-4 and 24-4±18-6). There was a positive correlation (r=0.81, p<0.02) between T cell cytotoxicity and the proportion of OKT8+ cells which was independent of therapy but confined to HBeAg positive patients.

In earlier studies with similar patients we have shown that there is a negative correlation between the proportion of OKT8+ cells and suppressor cell function in HBeAg positive cases and this, in conjunction with the present results, suggests that the increased proportion of OKT8+ cells reflects increased numbers of cytotoxic T cells in the peripheral blood and may be unrelated to any changes in suppressor cell function.

T17 Reactivity of anti-hepatocyte antibody RL23/36 with normal and abnormal human liver tissue

C J Hawkey, C H Holmes, E B Austin, B Gunn, M J Ebleston, R W Baldwin, P G Smith, and P J Toghill (University Hospital, Queen's Medical Centre, Nottingham, and Cancer Research Laboratory, University of Nottingham, Nottingham) We have developed a monoclonal antibody RL23/36 which reacts with an antigenic determinant expressed on the surface and in the cytoplasm of rat and human hepatocytes. We have studied its reactivity with histologically normal and abnormal human liver tissue.

Needle liver biopsies were obtained from 58 patients at diagnostic liver biopsy or at cholecystectomy. The reactivity of RL23/36 was examined on frozen sections using an indirect immunoperoxidase technique.

No reactivity was seen with cells other than hepatocytes. In 24 out of 25 histologically normal liver biopsies diffuse cytoplasmic binding of RL23/36 was observed in all hepatocytes. In histologically normal liver tissue from an insulin-dependent diabetic no binding occurred. Failure of binding also occurred in six of 33 histologically abnormal liver biopsies with the features of autoimmune liver disease (three), haemochromatosis (one), alcoholic liver disease (one), and liver tissue adjacent to a metastasis (one). RL23/36 did not bind to hepatoma tissue present in one liver biopsy.

Expression of the antigenic determinant with which RL23/36 reacts is lost during experimental hepatocarcinogenesis and in the only human hepatoma examined. Its loss in liver diseases associated with an increased risk of malignancy may lead to a deeper understanding of the pathogenesis of chronic liver disease and the development of malignancy.

T18 Liver graft rejection in the immunocompetent subhuman primate

O Epstein, P J Scheuer, M C Kew, and J A Myburgh (Royal Free Hospital Medical School and University of Witwatersrand Medical School, Johannesburg) The liver is considered 'immunologically privileged', and HLA matching is not considered a critical factor when considering suitability for liver transplantation. To test this hypothesis in primates we have retrospectively studied 120 liver-transplanted chacma baboons, none of which had received postoperative immunosuppression. Median survival was 28 days (range 0-390), and all animals surviving 14 days had biochemical evidence of marked cholestasis. At necropsy, only 11% had normal-looking livers. Necropsy liver biopsy specimens from 108 baboons were suitable for histological evaluation. Liver histology was normal in 12, and in 29 there were features consistent with septic cholangitis or shock. In 67 animals, there were features suggestive of liver rejection. These included mononuclear cell portal inflammation, damage to small calibre bile ducts with or without vascular damage, portal sclerosis, fibrous septum formation, and varying degrees of sinusoidal infiltration and cholestasis. Features of rejection usually occurred seven days after transplantation, and cirrhosis was present in 62% of 21 animals surviving 60 days. We conclude that, although liver cells are not a target for rejection, portal tract damage is common and results in cholestasis and rapidly developing cirrhosis.

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T19
HLA- A and B antigens in alcoholic and non-alcoholic chronic pancreatitis: is non-alcoholic chronic pancreatitis an autoimmune disease?

R A ANDERSON, D DONNAY, P DYER, AND J M BRAGANZA (Manchester Royal Infirmary, Manchester) HLA- A and B antigen frequencies were determined in 88 Caucasoids with chronic pancreatitis. The patients, who had been fully investigated, were divided into four groups depending on whether or not alcohol was an aetiological factor, and whether or not pancreatic calculi were detected by tomography. A detailed family history was obtained from all patients.

A and B antigen frequencies were not significantly different between the study group as a whole, compared with 344 controls. In the non-alcoholic group the frequency of HLA-A1 was significantly higher than in controls (134.7% compared with 34.8%; p 0.002, Fisher's exact test); the frequency of HLA-B8 was also higher but the difference did not reach statistical significance (38.9% compared with 27.9%). In the alcoholic group HLA-B21 occurred more frequently than in controls (13.8% compared with 2%; p 0.001). There was a much higher incidence of autoimmune disease in non-alcoholic patients and their close relatives than in the alcoholic group.

In conclusion: (1) the alcoholic and non-alcoholic varieties of chronic pancreatitis are associated with different HLA antigens; (2) the development of pancreatic calculi seems to be independent of tissue type; (3) HLA-A1 and B8 are well-established markers of autoimmune disease. The incidence of these antigens and of autoimmune diseases in the non-alcoholic group suggests a possible autoimmune basis for non-alcoholic chronic pancreatitis.

T20
Effects of neonatal antigen feed on subsequent systemic and local CMI responses

S STROBEL, AND A FERGUSON (Gastro-Intestinal Unit, Western General Hospital, and University of Edinburgh, Edinburgh) Systemic CMI is measured by intradermal skin tests; intestinal mucosal CMI can be detected by measurement of intestinal villi and crypts and intraepithelial lymphocyte counts. Adult mice given a single feed of the protein antigen ovalbumin (OVA) do not develop intestinal CMI, and have systemic hypo-responsiveness (oral tolerance) when subsequently parentally immunised and tested. We have tested the hypothesis that the age at first feed of a protein antigen influences subsequent immune responses: neonatal mice, aged 1 day, and adult mice were fed a weight-related dose of OVA or saline, by intragastric gavage. Four weeks later all mice were immunised with OVA in complete Freund's adjuvant and systemic immunity measured by serum antibodies and skin testing. Feeding of adult mice led to oral tolerance. Neonatal feeding led to priming of systemic humoral (+46%) and CMI responses (+26%). To test the induction of the local intestinal immune response, mice immunised as above were challenged with 2 mg% OVA in drinking water and mucosal morphology and IEL count measured. There was no evidence of mucosal CMI induction in adult mice. However, mice fed OVA on the first day of life and subsequently challenged had significantly high IEL counts when compared with saline fed ovalbumin challenged litter-mates (9.3 vs 14.6-100, p<0.005). These experiments show that protein feeding on the first day of life profoundly alters subsequent immune responses, causing priming of the immune system and induction of a local CMI response to the same antigen when presented later in life.

T21
Local immune responses preceding clinical relapse in ulcerative colitis: changes in Ig-containing cells, T-lymphocytes, and eosinophils

E LOPES PONTES, J PIRIS, D P JEWELL, AND S C TRUELOVE (Gastroenterology Unit, Radcliffe Infirmary, Oxford) Twenty patients with ulcerative colitis in complete clinical, sigmoidoscopic, and histological remission volunteered to be studied by regular monthly rectal biopsy over a period of six months while on no treatment. During remission, every patient had an excessive number of Ig-containing cells (especially IgG) and tissue eosinophils in the lamina propria. Eleven patients relapsed and in six of these a pronounced increase in the number of Ig-containing cells (especially IgG) occurred at least one month before the clinical relapse. Tissue eosinophils showed a similar pattern. By contrast, tissue neutrophils continued to be scanty at this stage and only became numerous at the stage of clinical relapse. In a similar study of 10 other patients, T-lymphocytes were demonstrated by an immunoperoxidase method using a monoclonal antibody (UCH T1). The T-lymphocytes resembled the Ig-containing cells in being raised even when the patients were in remission and in showing a further increase before and during clinical relapse. It is concluded that these patients with ulcerative colitis in remission show evidence of a continuous antigenic stimulation and that the immunological disturbance becomes more pronounced before a clinical relapse supervenes.

T22
Neutrophil luminescence in chronic inflammatory bowel disease (CIBD)

D KELLEHER, C FEIGHERY, AND D G WEIR (Departments of Immunology and Clinical Medicine, Trinity College, Dublin, and St James's Hospital, Dublin) Disorders of neutrophil chemotaxis have been described in chronic inflammatory bowel disease. Superoxide production by polymorphonuclear leucocytes can now be examined using bioluminescence techniques. Superoxide production by neutrophils stimulated with opsonised zymosan was measured in 29 patients with chronic inflammatory bowel disease as compared with 20 normal controls.

Patients with chronic inflammatory bowel disease had decreased superoxide production (49±28) as compared with controls (16±26; p<0.001). When eight patients with pure ileal disease were examined, however, their superoxide production was significantly higher (75±42) than patients with colonic disease (49±30), six of them lying within the normal range. The patients with colonic Crohn's disease had higher superoxide production than those with ulcerative colitis (30±20). No opsonisation defect was evident in these studies, as determined by zymosan opsonised with patient serum cross-reacting with control cells. To exclude the possibility that immune complex blockade of receptors was responsible for a soluble stimulant (formyl methionyl leucylphenylalanine) was added after maximal stimulation with opsonised zymosan. No further stimulation of activity was observed. The depression of neutrophil luminescence correlated with the severity of clinical disease. It is possible that patients with colonic inflammatory disease have an impaired superoxide production.
bowel disease have an intrinsic defect of neutrophil function, while those with terminal ileal disease are able to localise the disease effectively by a strong response from the phagocytes. It is more likely, however, that these results represent a secondary process analogous to neutrophil lysozyme depletion.

T23 Mucosal lymphocyte subpopulations in inflammatory bowel disease

W S SELBY, G JANOSY, M BOFILL, G GOLDSTEIN, AND D P JEWELL (Gastroenterology Unit, John Radcliffe Hospital, Oxford, and Department of Immunology, Royal Free Hospital, London) Lymphocyte subpopulations in the intestinal mucosa of patients with ulcerative colitis or Crohn's disease have been studied using a double marker immunofluorescence technique. In tissue sections, over 85% of intraepithelial lymphocytes (IEL) were T cells (HuTLA+ UCHT1+). The majority of these T IEL were of suppressor/cytotoxic phenotype (OKT8+: 83±2%), although only one-third of these reacted with another T cell antibody, OKT1. The remainder of the T IEL were of helper phenotype (OKT4+: 17±2%). No B lymphocytes were found within the epithelium. Within the lamina propria, OKT4+ T cells predominated (OKT4+: 62±1%; OKT8+: 38±1%). These findings did not differ from those seen in tissues from controls. However, in active inflammatory bowel disease the colonic epithelium, both surface and glandular, showed expression of HLA-DR antigens. This was not seen in inactive disease nor in control tissues.

In nine of the above subjects, lymphocytes were isolated from the intestinal lamina propria using an enzymatic technique. Although OKT4+ and OKT8+ T cell populations could be isolated from patients and controls, comparison with results from tissue sections indicated that the procedure tended to deplete OKT8+ cells.

These findings suggest that an imbalance of mucosal immunoregulatory T cells, as defined by monoclonal antibodies, does not occur in inflammatory bowel disease. The epithelial expression of HLA-DR antigens, however, may be of pathogenic importance. The results also indicate that functional studies of isolated intestinal lymphocytes should be interpreted with caution, and with reference to the results of morphological studies.

T24 Natural killer (NK) cells and their activity in intestinal mucosa

P R GIBSON, E L DOW, W S SELBY, D P JEWELL, AND R G STRICKLAND (Radcliffe Infirmary, Oxford) Mononuclear cells (MNC) isolated from the intestine display marked reduction or absence of natural killer cell activity when compared with autologous peripheral blood mononuclear cells. The present study examines possible mechanisms for this observation. Proportions of natural killer cells were determined in isolated intestinal mononuclear cells (enzymatic separation), mucosal tissue sections, and autologous peripheral blood mononuclear cells using the HNK-1 monoclonal antibody. Natural killer function of the isolated mononuclear cells from intestine and peripheral blood was studied in parallel using a four-hour 51Cr-release assay with K562 as the target cell. The effect of adjusting effector:target (E:T) ratios of intestinal mononuclear cells to approximate those existing in peripheral blood was examined.

Proportions of HNK-1+ intestinal mononuclear cells ranged from 1–3% compared with 7–19% HNK-1+ mononuclear cells in autologous peripheral blood. The paucity of HNK-1+ mononuclear cells in the intestine was confirmed by parallel study of tissue sections which also showed these cells to be located in lymphoid aggregates and lamina propria. Natural killer activity of intestinal mononuclear cells at E:T of 50:1 ranged from 0–5%; autologous peripheral blood natural killer activity at this E:T ratio was 18–38%. Adjustment of E:T ratios in intestinal mononuclear cells resulted in the appearance of significant natural killer activity (3–21%) in all experiments.

Previous observations of low or absent natural killer activity in intestinal mononuclear cells are probably attributable to low proportions of these cells in the mucosa. However, natural killer activity is demonstrable with these cells at high E:T ratios.

T25 Enhanced hepatic tumour growth after portal venous diversion

G JACOB, A K C LI, AND K E F HOBBS (Academic Department of Surgery, Royal Free Hospital School of Medicine, London) Whereas suggestions that deprivation of portal venous blood leads to regression of established liver tumours in clinical and experimental studies, the relationship of portal perfusion to initial tumour growth has not been fully investigated. We have studied the growth of implanted tumour in rat liver after portal venous diversion. Partial or complete portal venous diversion after staged portal vein occlusion was first confirmed in rats by corrosive casts. Serial liver histology and hepatic enzyme profiles were recorded in these animals (n=15). Immediately or at 48 hours after partial or total portal diversion, further rats (n=20) had a single inoculum...
of Walker carcinoma cells (5×10^6) injected into the liver. A control group (n=5) underwent sham surgery and received the same inoculum. Ten days later, the liver, tumour, and body weights were measured for each animal.

Although none of the rats had detectable biochemical or histological hepatic damage after staged portal vein diversion, animals inoculated 48 hours after total portal diversion showed increases in tumour/liver and tumour/body weight ratios (p=0.02, t-test).

We conclude that initial tumour growth is enhanced by specific alteration of portal blood flow. Since there was no hepato-cellular damage the tumour growth stimulation must be unrelated to factors which cause cellular proliferation under those conditions.

T27
Synthesis of lipoxygenase and cyclooxygenase products by human colonic mucosa

C J HAWKEY, N K BOUGHTON-SMITH, AND B J R WHITTLE (Department of Medicine, University Hospital, Nottingham, and Wellcome Research Laboratories, Beckenham, Kent) The human colon synthesises several prostanooids, which may have a role in inflammatory bowel diseases. As lipoxygenase products of arachidonic acid metabolism have been implicated in the inflammatory process, we have investigated the formation of both lipoxygenase and cyclooxygenase metabolites from [14C] arachidonic acid ([14C]-AA) by human colonic tissue.

Homogenates of human colonic mucosa were incubated with [14C]-AA and, after extraction into diethyl ether, separated by TLC using two solvent systems that allowed resolution of cyclooxygenase- and lipoxygenase products. Human colonic mucosa converted 10±3% (n=7) of the added [14C]-AA. The predominant cyclooxygenase products, identified by their chromographic mobility were, PGE_2 > PGF_2 alpha > PGD_2 > TXB_2 > 6-keto PGF_1 alpha. The formation of these products was inhibited both by indomethacin (1-10 μM) and the dual pathway inhibitor, BW755C (1-30 μM). The predominant lipoxygenase products formed, which had the chromatographic mobility of 11-12-15-HETE (which ran together) were inhibited by BW755C (30 μM) but not by indomethacin (3 μM). Using tissue from a colitic and a non-colitic patient, further resolution of the 11-12-15-HETE TLC band was performed using normal-phase HPLC. The non-colitic tissue formed predominantly 12-HETE, whereas both 12-HETE and 15-HETE were major products formed by the colitic tissue.

The present findings indicate that human colonic tissue can convert [14C]-AA into both lipoxygenase and cyclooxygenase products, as identified by chromatographic mobility and selectivity of inhibition by indomethacin and BW755C. The lipoxygenase products formed by human colonic tissue, including 15-HETE, may have a role in inflammatory bowel disease.

T28
Bacteril neuraminidase: a possible cause of relapse in ulcerative colitis

J M RHODES, RUTH GALLIMORE, Z J MOJADDEDI, R ALLAN, E ELIAS, AND J F KENNEDY (Departments of Medicine and Microbiology, General and Queen Elizabeth Hospitals, Birmingham, and Bioactive Carbohydrate and Protein Research Laboratory, Department of Chemistry, University of Birmingham, Birmingham) Histochemical studies in ulcerative colitis have shown abnormal substitution of sialic (neuraminic) acids in colonic mucus. This may cause reduced resistance to neuraminidase, so we are investigating the hypothesis that relapse of ulcerative colitis results from colonic overgrowth by neuraminidase-producing bacteria.

Faeces were sampled from 28 patients with ulcerative colitis, eight patients with Crohn's disease, and eight control subjects. Patients with ulcerative colitis were graded inactive, mild, moderate, or severe. Faeces were homogenised, centrifuged, and the supernatant filtered through 0.22 μm pore filters. Supernatant neuraminidase activity was assayed fluorimetrically and expressed as me-umbelliferyl units/g pellet wt where 1 unit=1 μmol of 4 me-umbelliferone released/hour at 37°C, pH 4.6 aD glucosidase was assayed fluorimetrically as a marker of bacterial exo-enzyme activity. As expected there was no significant difference overall in faecal neuraminidase between controls (56.6 u/g ± 56.1 SD), ulcerative colitis (44.9 u/g ± 52.8), and Crohn's disease (52.2 u/g ± 71.1). There was, however, a strong positive correlation between disease activity and faecal neuraminidase in ulcerative colitis: inactive mean neuraminidase 23.4 u/g, mild 22.3 u/g, moderate 39.1 u/g, and severe 87.6 u/g; t for B = O, 2.79; p<0.02. No significant difference in faecal α glucosidase was found between controls (24.4 u/g ± 34.7 SD), ulcerative colitis (28.6 u/g ± 23.6), and Crohn's disease (49.7 u/g ± 60.6). α Glucosidase did not alter with disease activity in ulcerative colitis so increased neuraminidase in active ulcerative colitis is not due to a non-specific increase in bacterial exo-enzymes.

These results support the hypothesis that relapse in ulcerative colitis is due to colonic overgrowth by neuraminidase-producing bacteria.

T29
Effect of bombesin on plasma cholecystokinin concentrations in normal subjects and patients with partial gastrectomy

J B M J JANSSEN AND C B H W LAMERS (Division of Gastroenterology, St Radboud Hospital, Nijmegen, The Netherlands) It has previously been shown that infusion of bombesin stimulates pancreatic enzyme secretion and gall bladder contraction. Several mechanisms for these actions have been suggested: direct effect of bombesin; activation of a duodeno-pancreatic reflex by bombesin; release of cholecystokinin by bombesin. We have measured plasma cholecystokinin concentrations during infusion of bombesin (100 ng/kg 20 min) in eight normal, seven subjects. In addition, eight patients with partial gastrectomy were studied in order to exclude an effect of bombesin-stimulated gastrin and gastric acid on cholecystokinin-release. Plasma cholecystokinin was measured by a specific and sensitive radioimmunoassay. The antibody used was directed against the mid-portion of cholecystokinin and did not show any cross-reactivity with gastrin.

Infusion of bombesin induced significant increases in plasma cholecystokinin in both normal subjects and gastrectomised patients. There was no significant differences between basal plasma cholecystokinin (1.2±0.3 vs 1.4±0.3 fmol/l), bombesin-induced increases in plasma cholecystokinin (6.6±1.1 vs 5.7±1.0), and integrated plasma cholecystokinin during infusion of bombesin (72.4±12.4 vs 92.6±21.1 fmol/ml/20 min). During infusion of bombesin serum gastrin increased from 16.7±1.4 to 49.6±8.1 fmol/ml (p<0.005) in the normal subjects, while there was no significant change in serum gastrin in the antrectomised patients.

We conclude that bombesin releases...
cholecystokinin in man by a gastrin-independent mechanism.

T30
Glucose and insulin levels in duodenal ulcer disease before and after surgery
R J CADE, G H LESTER, G R PHILPOT, AND L R CELESTIN (Departments of Gastroenterology and Biochemistry, Frenchay Hospital, Bristol) The aim of this study was threefold: to investigate glucose and insulin patterns in a group of patients with chronic duodenal ulceration (1) before surgery and (2) after surgery, and (3) to examine the effect of a glucosidase inhibitor (Acarbose) on any postoperative changes.

Ten males with proven chronic duodenal ulcers and 10 male volunteers were each given a standardised breakfast and venous blood samples collected every 15 minutes for two hours. Seven of the former group were retested after selective vagotomy and pyloroplasty on two separate mornings, on one of which they were given 100 mg Acarbose with the breakfast.

Glucose concentrations in the duodenal ulcer group were significantly higher than controls at 45, 60, and 90 minutes (p<0.05). The integrated response was also higher (p<0.005). There was no significant difference in insulin levels.

After surgery there was an early exaggerated peak in the glucose curve which did not reach statistical significance. From 45 to 120 minutes, however, glucose levels were significantly lower than preoperatively (p<0.05). Insulin levels were significantly higher postoperatively from 0 to 45 minutes (p<0.01), but differences in the later part of the curve were not significant.

Acarbose attenuated both hyper- and hypoglycaemic phases of the glucose curve, and decreased the insulin response throughout the study period.

Duodenal ulcer patients, therefore, have an abnormal glucose tolerance which is exacerbated by surgery and which, after surgery, is improved by Acarbose.

T31
Cholecystokinins in human small intestine: distribution of molecular forms
P N MATON, A C SELDEN, AND V S CHADWICK (Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) Knowledge of the distribution of various forms of cholecystokinins (CCKs) in human intestine is limited and the similarity of human and porcine cholecystokinins remains questionable. Accordingly we analysed the distribution of various forms of cholecystokinin throughout the small intestine.

Samples were washed in saline and stored at -20°C before processing. Mucosal and muscle layers were separated and each boiled in water to extract cholecystokinins. The supernatants were subjected to two-step reverse phase high-pressure liquid chromatography and samples analysed using (1) a 'non-specific' radioimmunoassay detecting the carboxyl-terminal of all cholecystokinins and gastrins and (2) a gastrin-specific assay.

Total cholecystokinin immunoreactivity in mucosal samples was 137 ng CCK 8 equivalents/g in jejunum, 23 ng/g in mid small intestine and <1 ng/g in terminal ileum. The majority of mucosal cholecystokinin (66-76%) co-chromatographed with porcine CCK 8. A second peak of immuno-reactivity (16-17% of total) co-chromatographed with porcine CCK 33/39. Assuming similar cross-reactivities of porcine and human cholecystokinins within the assay, the molar ratios of CCK 8:CCK 33/39 were 1.9-2.2:1. Jejunal muscle contained 13 ng CCK/g, principally co-chromatographing with CCK 8. Cholecystokinins were not detected in the remainder of small intestinal muscle (<1 ng/g).

We conclude that (1) human and porcine intestinal cholecystokinins have similar hydrophobic properties; (2) most mucosal cholecystokinin is CCK 8-like and together CCK 8 and 33/39-like peptides constitute 85% of total cholecystokinins; (3) only small amounts of cholecystokinins are present in the muscle layers of human small intestine.

T32
Cephalic phase of pancreatic secretion in man: effects of sham feeding with and without atropine
A A ANAGNOSTIDES, P N MATON, AND V S CHADWICK (Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) The relative importance of neurogenic and hormonal influences on pancreatic secretion in man is disputed. In order to examine the role of vagal stimuli we studied the effect of sham feeding on pancreatic outputs.

After an overnight fast five normal volunteers underwent a secretin-caerulein test (secretin 1 CU/kg and caerulein 100 ng/kg) using duodenal perfusion with gastric aspiration to measure both basal and 'maximal' pancreatic secretory outputs of trypsin, bicarbonate, and fluid. On another occasion a 40 minute period of sham feeding (chewing and spitting bacon sandwiches) was used instead of exogenous stimulation. On a third occasion the sham feeding study was repeated after administration of atropine (0-6-1-2 mg intravenously).

Basal and 'maximal' outputs of trypsin were 743±441 (SD) and 3475±576 IU/30 min respectively. Output during sham feeding was 3192±1045 (p<0.001 vs basal) equivalent to 92% of 'maximal'. Atropine suppressed basal output to 112±59 (p<0.001) and output during sham feeding to 489±389 IU/30 min (p<0.001). A similar result was observed with fluid secretion. Basal and 'maximal' outputs of bicarbonate were 0-9±0-7 and 22±21 mmol/30 min respectively. Sham feeding produced only a modest increase in bicarbonate secretion to 3-3±2 (15% of maximal). Atropine produced no significant reduction in basal or sham feeding stimulated bicarbonate secretion.

We conclude that (1) there is tonic vagal stimulation of pancreatic trypsin secretion in the fasting state; (2) sham feeding produces near 'maximal' secretion of both trypsin and water; (3) vagal stimuli are of little importance in bicarbonate secretion.

T33
Trypsin secretion in response to endogenous and exogenous stimulation in chronic pancreatitis
H J KLASS, G I SANDLE, P KAY, P DAVIES, AND J M BRAGANZA (Manchester Royal Infirmary, Oxford Road, Manchester) Studies in volunteers and patients without pancreatic disease showed that the mean trypsic activity in duodenal juice after a Lundh meal approximated the peak trypsic activity after intravenous injection of pancreozym (2 CHRu/kg). In patients with chronic pancreatitis mean trypsic activity was disproportionately reduced compared with peak trypsic activity – a phenomenon which could reflect impaired release of CCK-PZ from the intestinal mucosa, or excessive dilution of the secreted pancreatic enzymes. We distinguished between these two possi-
bilities by comparing the output of trypsin after endogenous and exogenous pancreatic stimulation using validated double-marker techniques in five volunteers and seven patients with chronic pancreatitis.

The mean 10-minute trypsin output after a test meal was similar to the peak 10-minute trypsin output after pancreaticozymin in both groups. The cumulative volume of gastric contents emptied into the duodenum two hours after the meal was significantly higher in the chronic pancreatitis group. In three patients with chronic pancreatitis gastric acid hypersecretion was apparent, but there were no differences overall in the cumulative duodenal acid load, or duodenal pH between the two groups.

We conclude that the disproportionate reduction in mean tryptic activity compared with peak tryptic activity in chronic pancreatitis is not due to impaired release of CCK-PZ, but to excessive dilution of the secreted pancreatic enzymes.

**T34**

**Studies of the gastric ‘mucus-bicarbonate’ barrier: the influence of prostaglandin on the pH gradient across rat gastric mucus in vivo**

I N ROSS AND L A TURNBERG (Department of Medicine, Hope Hospital, Salford) Previous studies have demonstrated a pH gradient across the mucus layer adherent to gastric mucosa indicating the existence of a ‘mucus-bicarbonate’ barrier. We have now investigated the maximal pH in the mucus layer which the mucus can produce and the effect of a ‘cytoprotective’ prostaglandin. Using an antimony chloride pH microelectrode, tip diameter 50 μ, the maximal pH recorded in the mucus on anaesthetised rat gastric mucosa in vivo was determined after adjusting luminal pH to 7 with phosphate buffer (n=5). The maximal pH rose above luminal pH to 7.88±0.2 (range 7.59 to 8.08), which is significantly higher than luminal pH (6.85±0.33; p<0.001). This intramucosal pH must be close to that of basal secretion of the surface mucosa. In eight rats given 25 μg of 16,16 dimethyl prostaglandin E2 (DMPGE) subcutaneously the mean maximal pH recorded in the mucus layer was 7.89±0.45 compared with 7.43±0.56 in untreated rats (p<0.05), when luminal pH was 2. Luminal application of aspirin (20 mmol) dropped the intramucous pH in seven of eight untreated rats but in eight rats treated with DMPGE only two showed any fall on exposure to aspirin. Mean intramucous pH fell from 6.9 to 6.85 in treated rats and from 6.8 to 5.3 in untreated rats (p<0.005). DMPGE did not prevent the fall in intramucous pH induced by N-acetyl cysteine or luminal pH 1-4 HCl.

These results suggest that the pH of the fluid secreted into mucus is alkaline (mean pH 7.88) and that prostaglandins enhance this alkaline component and prevent dissipation of the gradient by aspirin. These observations support a role for the ‘mucus-bicarbonate’ barrier in mucosal protection.

**T35**

**Effect of a mast-cell stabilising agent on gastric acid secretion in response to pentagastrin in conscious dogs**

S P CANFIELD AND B P CURWAIN (introduced by D L Wingate) (Department of Physiology, St Mary’s Hospital Medical School, London) FPL 52694 stabilises mast-cells and has been shown to inhibit pentagastrin stimulated secretion in anaesthetised, pylorus ligated rats and dogs. We have studied the effect of FPL 52694 in conscious beagles with gastric fistulae during continuous intravenous infusion of pentagastrin (2 μg/kg/h). In one series of experiments FPL 52694 (5 or 10 mg/kg/h) was added to the intravenous infusion after 90 minutes for the next 60 minutes. Results were similar at both doses and a maximum inhibition of acid output of 53±8% mean, SEM, n=4) was seen after 45 minutes. The volume of secretion was reduced to a lesser extent (30±10%) and the [H+] mean in the juice was reduced by 28±10%. In control experiments there were no significant changes in any parameter. In a second series FPL 52694 was given intragastrically (4.5 mg/ml in distilled H2O given as 4x10 ml aliquots over 30 minutes with the fistulae closed) 90 minutes after beginning intravenous infusion of pentagastrin. The fistulae were then opened, the stomachs allowed to drain and secretion followed for a further 60 minutes of pentagastrin infusion. Maximum inhibition of acid output was 90±4% (n=5) after 15 minutes and was 74±6% after 60 minutes. At 15 minutes the volume of secretion was reduced by 60±12% and [H+] by 79±5%.

FPL 52694 inhibits pentagastrin stimulated acid secretion in conscious dogs and is more potent when given intragastrically than intravenously. The possibility that mast-cell stabilising agents offer an alternative method for control of gastric acid secretion merits further investigation.

**T36**

**Inhibition of gastric acid secretion by AH22216, a new long-acting histamine H2-receptor antagonist**

J M HUMPHRAY, M J DALY, AND R STABLES (introduced by J J Misiewicz) (Glaxo Group Research Limited, Ware, Hertfordshire) AH22216 is a new, potent histamine H2-receptor antagonist with a prolonged duration of action; it differs qualitatively from cimetidine and ranitidine in that it does not appear to behave competitively in vitro.

The antisecretory activities of AH22216 and ranitidine have been compared in the dog. AH22216 was four to 10 times more potent than ranitidine as an inhibitor of gastric acid secretion induced by histamine or pentagastrin in the Heidenhain pouch of the dog (n=5). Antisecretory ED50 values in mg/kg (95% confidence limits) for AH22216 were 0.019 (0.016-0.025) intravenous and 0.029 (0.025-0.033) p.o. vs histamine, and 0.025 (0.020-0.029) intravenously and 0.049 (0.034-0.066) p.o. vs pentagastrin. AH22216 0.03-0.10 mg/kg intravenously, inhibited the secretory response to a test meal in dogs (n=3) with a gastric fistula. The duration of action of AH22216 was very prolonged compared with that of ranitidine. At 1 mg/kg p.o., ranitidine inhibited histamine-induced gastric acid secretion by 95±2% at two hours, 62±8% at four hours and 23±9% at eight hours, whereas an equipotent dose of AH22216, 0.10 mg/kg p.o., inhibited secretion by 67±9% at two hours, 95±3% at four hours, 89±2% at eight hours, 54±8% at 18 hours, and 32±13% at 24 hours. In a separate series of experiments in the dog, secretory dose-response curves to histamine were displaced in a parallel, dose-related manner by AH22216, indicating competitive antagonism.

In summary, AH22216 is a potent, long-lasting inhibitor of gastric acid secretion in the dog, and warrants investigation in man.
F1 Surgical treatment of gastro-oesophageal reflux by partial fundoplication (Lind procedure)

C J STODDARD AND J A R SMITH (University Surgical Units, Royal Liverpool Hospital, Liverpool, and Royal Hallamshire Hospital, Sheffield) The Belsey Mark IV and Nissen procedures are effective operations for the control of gastro-oesophageal reflux (GOR) but may be followed by dysphagia, gas bloat syndrome, and recurrence. We have evaluated a technique of transabdominal partial fundoplication, the Lind procedure, in 25 patients with gastro-oesophageal reflux.

All patients had symptoms of gastro-oesophageal reflux which had failed to respond to medical treatment, radiological evidence of reflux, and endoscopic histological evidence of oesophagitis. Patients underwent clinical, radiological and manometric evaluation pre- and postoperatively. A transabdominal 270° partial fundoplication was performed in all patients and in three patients this was combined with simultaneous dilatation of an oesophageal stricture and with vagotomy for duodenal ulceration in three others. Five patients required splenectomy for intraoperative splenic trauma.

At a six months’ postoperative assessment no patients were suffering from heartburn, acid regurgitation, or the gas bloat syndrome. Five patients had experienced a transient dysphagia in the immediate postoperative period. Gastro-oesophageal reflux was still present radiologically in only one patient. Postoperatively, there was a significant rise in pressure at the lower end of the oesophagus p<0-01. We conclude that this is a satisfactory technique for the control of gastro-oesophageal reflux.

F2 Cholecystectomy and vagotomy – an unhappy combination?

M W N WARD, C G CLARK, AND D KARANANOLIS (Department of Surgery, University College London, the Rayne Institute, University Street, London) Gall stones and duodenal ulcer coexist in some 10% of duodenal ulcer patients requiring surgery, and it has been shown that there is a high incidence of post-vagotomy diarrhoea when these patients are treated by combined cholecystectomy and truncal vagotomy and pyloroplasty. There are, however, no reports of the outcome of combining cholecystectomy with PGV. We have therefore compared the results of surgery in 64 patients subdivided into four matched groups; (1) PGV, (2) PGV + cholecystectomy, (3) TV + PY, (4) TV + PY + cholecystectomy.

There was no diarrhoea after PGV alone but when combined with cholecystectomy diarrhoea occurred in 30% of patients. For TV + PY, diarrhoea occurred in 25% but when combined with cholecystectomy this figure increased to 60%, with a greater proportion of more troublesome diarrhoea. The aetiology of post-vagotomy diarrhoea is speculative but some form of bile acid malabsorption may be responsible. This view is supported by observations comparing the outcome of PGV with and without cholecystectomy. Whichever combination of operation is used for treatment there is an increase in post-vagotomy diarrhoea, but the lesser of the two evils appears to be the combination of cholecystectomy with PGV.

F3 Infection after cholecystectomy in a provincial district hospital

A FLOWERDEW, D BADENOCH, AND R G FABER (Department of Surgery, Battle Hospital, Reading) This prospective study was made of 183 consecutive patients admitted under the care of one surgeon. The objects were to determine (1) the incidence of organisms in the bile and its relationship to infection; (2) the incidence of systemic and wound infection; (3) the effects of certain clinical factors on infection and organisms in bile.

For analysis the patients were divided into four groups: group I: 162 patients undergoing planned cholecystectomy only; group II: eight patients undergoing semi-emergency cholecystectomy; group III: 22 patients undergoing unexpected exploration of bile ducts; group IV: 19 patients with obstructive jaundice due to stones.

Forty-five patients (23%) had positive bile cultures; group I, 18 (13%); group II, five (63%); group III, 10 (45%); group IV, 12 (63%). One patient in group IV developed septicaemia despite having prophylactic antibiotics. No patient developed intra-abdominal infection. Twenty-two patients (12%) developed wound infections: group I, 11 (7%); group II, two (25%); group III, five (23%); group IV, four (21%). In only six patients, however, (27% of wound infections, 3% of whole series), was the same organism cultured from wound and bile. In group IV two wound infections occurred in 11 patients given prophylactic antibiotics, while two infections occurred in eight who were not.

Contrary to previous reports, the incidence of systemic and wound infection is lower, and organisms in the bile rarely cause infection.

F4 Management of portal hypertension and post-cholecystectomy bile duct strictures

C J KELLEY, G A D MCPHERSON, AND L H BLUMGART (Hepatobiliary Surgical Department, Hammersmith Hospital, and Royal Postgraduate Medical School, London) Damage to the biliary tree occurs once in every 400 cholecystectomies and if uncorrected will result in biliary obstruction and biliary fibrosis. Portal hypertension will then develop in a significant proportion of patients especially if the obstruction is prolonged and associated with frequent episodes of cholangitis. Both of these factors may be influenced by the number of previous attempts at establishing biliary drainage. Once portal hypertension is established subsequent stricture repair is associated with a high mortality.

Of 69 patients referred with such strictures nine (13%) had portal hypertension. Eight patients had multiple laparotomies before referral and all had recurrent cholangitis. Five patients had clinically evident portal hypertension, three were diagnosed on either endoscopy or angiography, and one at laparotomy. Four patients had portasystemic anastomoses, one with a simultaneous hepaticejunostomy. Four had hepaticejunostomy alone and one had a laparotomy at which no procedure was possible. Five patients have subsequently died of liver failure.

If biliary bypass is performed early in the course of the disease portal hypertension may regress. After prolonged obstruction, however, a portasystemic shunt may be necessary to lessen peroperative complications. Portal hypertension must therefore be considered in all patients with benign strictures and confirmed by endoscopy and angiography when necessary. Early diagnosis is essential when planning the appropriate treatment, which may still be associated with a high mortality.
F5 Prolonged irrigation of the pancreatic bed after debridement for severe necrotising pancreatitis

N J MCC MORTENSEN AND H J ESPINER (Department of Surgery, Bristol Royal Infirmary, Bristol) The mortality from severe necrotising pancreatitis may approach 70%, and the survivors often require repeated operations to debride the pancreas and drain abscesses. We report the results of prolonged irrigation of the pancreatic bed after surgical debridement in nine patients with severe necrotising pancreatitis. Patients with pancreatic abscess or pseudocyst presenting later in their clinical course have been excluded.

All nine patients were critically ill with hypoalbuminaemia, leucocytosis, and a falling haemoglobin (mean 3.9 g/dl). At definitive surgery an average of 17 days (range eight to 25 days) after onset of symptoms the pancreatic slough was thoroughly debrided and two or more large drains were placed in the pancreatic bed. Irrigation with saline (2 l/day) was started after two days and continued for a mean of 23 days (range 10–54 days).

There were two deaths, five and 25 days after surgery, and one of these patients required packing for massive postoperative haemorrhage. No other patient required further surgery. Four patients developed fistulae (one gastric, three biliary) which all closed spontaneously.

After thorough debridement and drainage, prolonged irrigation of the pancreatic bed may reduce mortality and the need for repeated drainage procedures in patients with severe necrotising pancreatitis.

F6 Identification of patients with ‘occult’ complications of acute pancreatitis

A D MEYER, M J MCMAHON, MARGARET BOWEN, AND E H COOPER (University Department of Surgery, General Infirmary, Leeds, and Unit for Cancer Research, University of Leeds, Leeds) Patients who develop pancreatic collections (pseudocyst or abscesses) after an attack of acute pancreatitis are frequently discharged from hospital without the presence of complication being suspected. In this study markers of continuing inflammation have been evaluated in order to select those which might be useful to screen patients for these complications.

Body temperature, leucocyte count (WBC), ESR and plasma levels of C-reactive protein, α1-protease inhibitor and anti-chymotrypsin were measured during the initial 13 days in hospital in 53 patients with acute pancreatitis. Sixteen patients had an attack defined as severe and 11 of them developed a pseudocyst or abscesses. The initial part of the illness was clinically mild in seven of the patients who developed complications, and the measured parameters showed only limited discrimination between severe and mild attacks during the first five days. Between five and 13 days 95% confidence limits for C-reactive protein in severe attacks showed complete separation from those for mild ones. The leucocyte count also had predictive power but other parameters were less useful.

This study suggests that (1) pancreatic collections originate early during the course of acute pancreatitis, (2) measurement of C-reactive protein in the second week of pancreatitis can select patients in whom pancreatic collections are developing.

F7 Intestinal microcirculatory changes in the normal and diseased bowel

N D CARR, B PULLAN, AND P F SCHOFIELD (Teaching Unit Five, Withington Hospital, University Hospital of South Manchester) Several papers have reported similarities between colonic ischaemia and inflammatory bowel disease in older patients. Occlusive vascular changes have been noted in the small intramural intestinal vessels in inflammatory bowel disease. We have investigated and quantified the intestinal microcirculation in the normal and abnormal from excised specimens of bowel. The specimens were perfused with barium sulphate suspension, which penetrates to the smallest intramural vessels. The concentration of barium has been estimated using an x-ray fluorescence method in tissue blocks of resected bowel.

Twenty-one control cases, eight patients with Crohn’s disease, three patients with ulcerative colitis, five patients with radiation bowel damage, and two patients with colonic ischaemia have been studied.

Our results indicate that: (1) there is a highly significant negative correlation (p<0.002) between the concentration of barium and age in the normal group (r=-0.73); (2) the Crohn’s disease group shows a highly significant reduction in the concentration of barium (p<0.001); (3) a similar reduction in the concentration of barium was seen in radiation enteritis and ischaemic colitis (p<0.001).

This reduction in microcirculatory volume may play a role in the pathogenesis of Crohn’s disease, radiation bowel damage, and colonic ischaemia, but not in ulcerative colitis.

F8 Prevention of peritoneal adhesions after thermal injury using the formaldehyde carriers noxythiolin and taurolin

D J LEAPER AND A KAPLUN (introduced by R C N Williamson) (Departments of Surgery, Westminster Hospital and Bristol Royal Infirmary) Although postoperative peritoneal adhesions have become the commonest cause of intestinal obstruction many adhesions may be protective in walling off vulnerable suture lines, damaged bowel, or inflammatory collections.

In this study mice were submitted to laparotomy under intravenous nembutal anaesthesia. An unperfused method of producing a measurable peritoneal adhesion was assessed by subjecting the caecum of each mouse to a thermal injury of 69°C for 5 s using a water heated 2.5 mm brass disc. Before abdominal closure groups of mice had 0.1–0.75 ml isotonic saline (controls) or 2.5–6.25 mg noxythiolin or taurolin in similar amounts of saline instilled intraperitoneally. All mice were killed seven days later and peritoneal adhesions examined without knowledge of the treatment groups. 61/65 controls developed an adhesion to the caecal burn compared with 41/66 in the noxythiolin treated mice (p<0.001) and 49/68 in the taurolin treated mice (p<0.002). There was no macroscopic evidence of caecal dehiscence or bacterial contamination from the burn site.

The formaldehyde carriers noxythiolin and taurolin have both been shown to inhibit the formation of peritoneal adhesions produced by thermal injury. On the surgical occasions where adhesion formation should be minimised, as in general bacterial peritonitis, it is suggested that intraperitoneal instillation of noxythiolin or taurolin may be of clinical value as an adjunct to meticulous surgical technique.
F9
Non-invasive assessment of intestinal ischaemia
B H WALMSLEY, J S FLEMING, AND S J KARRAN
(University Surgical Unit and Department of Nuclear Medicine, Southamton General Hospital, Southamton) The diagnosis of mesenteric ischaemia is often difficult and delay in surgical intervention may prejudice the outcome. We have developed a non-invasive technique, using dynamic hepatic scintigraphy after a bolus injection of 99mTc sulphur colloid, which is able to assess the portal component of total hepatic blood flow. The ability of this method to detect reduction in mesenteric flow following progressive mesenteric ischaemia was examined.

Thirty-five Wistar rats were studied in five groups of seven animals: group 1, control; group 2, sham operation; group 3, ligation of ileocolic artery proximal to the terminal caecal branch; group 4, ligation of superior mesenteric artery distal to the origin of the middle colic artery; group 5, ligation of superior mesenteric artery proximal to the origin of the middle colic artery.

Mesenteric blood flow in the control animals was 72% ± SD 3-2 of total hepatic flow and this value did not differ significantly in the sham operated group. Mesenteric flow fell to 58% ± SD 3-8 in group 3 (p<0.01). A further fall to 52% ± SD 6-8 was seen in group 4. The reduction in flow was greatest in group 5 animals, 32% ± SD 8-7 (group 4 vs group 5 p<0.01). Total liver blood flow was also progressively reduced from groups 2 to 5.

As this imaging technique can be used clinically, the results of this study suggest that it may be of value in the diagnosis and assessment of patients with mesenteric ischaemia.

F10
Conservative treatment of fissure-in-ano
M J GOUGH AND A A M LEWIS
The Royal Free Hospital, London) Posterior fissure-in-ano (PFIA) is an exquisitely painful condition for which conservative treatment with a topical local anaesthetic and a St Mark’s Hospital anal dilator is widely used. The rationale for using the dilator, which may be both painful and distasteful to the patient, is difficult to understand. The value of such therapy has therefore been assessed in a randomised clinical trial of 82 patients with a PFIA. Within one month healing occurred in 17/39 patients (43-6%) treated with lignocaine gel alone compared with 18/43 patients (41-9%) who also used the dilator. The mean duration of symptoms was the same in both groups. The success of both methods of treatment in PFIA present for less than three months (50%) was no different from that in fissures of longer standing (40%, χ²=0-6458). As this trend was reversed if the results were reconsidered with a six month cut-off, there is no evidence to suggest that conservative therapy for PFIA should be reserved for fissures of short duration.

On the basis of these results it is suggested that the use of an anal dilator in the management of PFIA is abandoned in favour of treatment with anaesthetic gel alone, and early surgical intervention if necessary.

In 12 of 15 patients with an anterior fissure-in-ano there was an obvious predisposing factor. Resolution of underlying anal pathology was presumably responsible for the greater success (73.3%) of a similar period of conservative treatment in these patients.

F11
Anal manometry in neuropathic faecal incontinence and complete rectal prolapse
M PESCATORI, G G P BROWNING, AND A G PARKS
(Surgical Research Department, St Mark’s Hospital, London) Previous work suggests that in patients with pelvic floor neuropathy combined faecal incontinence and complete rectal prolapse is associated with more severe sphincter deficiency than incontinence alone.

Seventy-two patients with electrophysiological evidence of primary neuropathic faecal incontinence were studied. Group 1 consisted of 33 patients (46%) with faecal incontinence accompanied by complete rectal prolapse; group 2 comprised the remaining 39 patients (54%) with faecal incontinence alone. Anal canal pressures and rectal capacity were measured and compared in these two groups of patients.

Mean anal canal length did not differ significantly; 2-4±0.6 cm in group 1 and 3-1±1-1 cm in group 2 (mean ± SD, χ²-test, pNS). Anal pressures were less in group 1; mean resting pressure was 31±19 cm water in group 1 and 43±23 cm water in group 2 (p<0.05) and mean squeeze pressure 24±17 cm water and 41±29 water respectively (p<0.02). Mean rectal capacity in group 1 was 155±71 ml and in group 2 200±49 ml; this difference was not significant (p NS).

These results confirm previous reports of greater anal sphincter deficiencies when neuropathic faecal incontinence is accompanied by complete rectal prolapse. Further studies are required to quantify this by electrophysiological means.

F12
Results of delayed anal sphincter muscle repair for trauma
G G P BROWNING AND A G PARKS
(Surgical Research Department, St Mark’s Hospital, London) Ninety-two patients, 38 men and 54 women, have been treated by delayed anal sphincter muscle repair for traumatic sphincter division. The aetiology was operative injury in 53 (M21, F32), trauma in 26 (M17, F9), and obstetric injury in 13 patients. Sixty (65%) patients presented with frank faecal incontinence of 8-0±3-0 years (mean ± SEM) duration in the men and 11±5±1-6 years in the women (p<0.05). The remaining 32 (35%) patients had stomas performed at the time of injury 2-6±0-5 years before repair.

In all cases the sphincter muscle ring was repaired by an overlapping technique protected by a temporary loop colostomy; four patients had combined sphincter muscle repair and post anal repair. There was no postoperative death. Complications occurred in 25 patients and included sinus, 12; stricture, eight; fistula, three; and necrosis, two. Two of these patients required revision of the repair within one month.

Closure of colostomy has been carried out in 79 patients; 10 await closure. Function has been assessed in 73 from three to 114 months (mean 30-1 months) afterwards. Sixty-two (86%) patients regained full continence apart from minor problems with flatus and the remaining 11 (14%) have normal control provided the stool is solid. The repair failed on three occasions; one patient had a successful second repair but two required permanent colostomies.

The operation is straightforward, has a low morbidity and mortality, and produces good functional results.
F13 Results of colectomy for slow-transit constipation

D M PRESTON, P R HAWLEY, J E LENNARD-JONES, AND I P TODD (St Mark’s Hospital, London) From 1969–82, 96 adults with chronic constipation were treated by bowel resection; 43 had Hirschsprung’s disease and 35 idiopathic megacolon. We report the results in 18 patients with an apparently normal colon but greatly reduced whole gut transit rate. All were female, with mean age at operation 25 years. They were incapacitated by abdominal symptoms; three had no spontaneous bowel actions and the interval between bowel actions in the others ranged from seven to 35 days. Operation was advised as a last resort after failure of medical treatment. Thirteen were treated by subtotal colectomy (seven caecorectal and six ileorectal anastomosis), two by sigmoid colectomy, two by left hemicolectomy, and one by Duhamel’s procedure. There were no deaths or operative complications. Over a mean follow-up of 4.5 years (range six months to 11 years), six have experienced episodes of small bowel obstruction, three of whom needed laparotomy (all IRA).

No patients treated by sigmoid colectomy or left hemicolectomy was improved. Of the 13 patients who had subtotal colectomy, the result was satisfactory in 10. Constipation was relieved in seven (bowels open >1x daily) and the other three were improved, though are still constipated and need laxatives. Three patients were not helped; two still cannot defaecate and one has diarrhoea probably due to laxative addiction.

Subtotal colectomy, but not partial colectomy, with removal of an apparently normal colon, can benefit women with severe intractable constipation.

F14 Prognostic factors in operable rectal cancer, as seen in the United Kingdom

A N SMITH, L S FREEDMAN, AND W DUNCAN (Departments of Surgery and Radiation Oncology, University of Edinburgh, and MRC Cancer Trials Office, Cambridge) The opportunity arose of studying 824 cases of operable rectal cancer entered into an MRC trial of irradiation in operable cancer of the rectum. The cases had been contributed from 17 centres widely scattered in the UK, thus giving a picture, not of the disease in any one hospital or region, but in the country as a whole. There were significant relationships between the prognosis and the fixity of the tumour, its Dukes’ stage and the histological grade. Tumours less than 8 cm from the anal verge had a poorer prognosis than higher ones. There was a greater frequency of recurrence in older patients but no indication of a sex difference in prognosis. The highest proportion of mobile tumours was in the Dukes’ A group and of fixed tumours in the Dukes’ B, with Dukes’ C equally fixed or mobile. There was a positive relationship between the quadrants involved and fixity. The protocol of the trial was designed to recruit operable cases; yet only 49% of such cases in the UK were mobile tumours. The mobility of the tumour was of great prognostic significance: 80% of mobile tumours had curative resections. The three year survival of 401 mobile tumours was 58% compared with 36% for 364 tethered tumours. The survival rate at three years in Dukes’ stages A, B, and C showed the expected high survival in the more favourable A cases. The local disease-free rate was also closely related to Dukes’ staging being at three years, 81%, 65%, and 51% for Dukes’ A, B, and C respectively. Fifty-eight per cent of patients with histological low grade tumours were alive and free of disease at three years compared with 24% of patients with high grade lesions.

F15 Jejunal motility in patients with functional abdominal pain

J KINGHAM, R BOWN, ELSPEITH BELLHOUSE, AND A M DAWSON (Gastroenterology Department, St Bartholomew’s Hospital, London) There is now accumulating evidence to suggest a disturbed colonic motility pattern in patients with functional abdominal pain. In addition preliminary observations with a single radiotelemetry pressure-sensitive capsule have suggested that there may be a disturbance of small gut motor pattern in the irreducible bowel syndrome. Using paired, tethered, radiopill 20 cm apart we have studied jejunal motor activity in six patients presenting with abdominal pain in the irritable bowel syndrome and 10 matched controls. The pills were screened into the jejunum with the proximal pill at the duodenjejunal flexure and fasting, fed, and sleep recordings obtained for up to 30 hours.

We recorded the duration of proximal phase III complexes (5.39±2.03 min for normal subjects, 5.33±1.83 min for those with the irritable bowel syndrome), the duration of distal phase III complexes (5.70±2.62 min for normal subjects, 5.59±2.15 min for those with the irritable bowel syndrome), the speed of propagation (3.15±3.44 min for normal subjects, 4.09±5.82 min for those with the irritable bowel syndrome), the frequency of migrating motor complexes, (96±49.94 min for normal subjects, 77±51.63 min for those with irritable bowel syndrome).

In both groups 7% of phase III activity appeared only at the proximal radio-pill with 26% in both groups appearing only at the distal pill. Two migrating motor complexes exhibited retrograde propagation. Feeding usually, but not invariably, delayed the first migrating motor complexes in both groups but after food the return of phase III activity was often seen only at one locus. During sleep type II activity was reduced but phase III activity remained unchanged in both groups. There was no correlation between either phase II or III motor activity and abdominal pain in the irritable bowel group.

These studies demonstrated a marked variability in the pattern of phase III activity (migrating motor complexes) within and between normal subjects and a similar variability in patients with functional abdominal pain. No difference could be elicited between the two groups contrary to previous reports.

F16 Antral gastrin cell hyperplasia

N A LØVGRÉN, P DELIKARIS, J POULSEN, L I LARSSON, AND E AMDRUP (Surgical Gastroenterological Department L, Aarhus Kommunehospital, Aarhus, Denmark) Hypergastrinemia due to gastrinoma is a well-established clinical entity, but non-tumorous hypergastrinaemia of antral origin, associated with duodenal ulceration has not yet been universally accepted.

This paper describes three cases of ulcer recurrence where antral G-cell hyperplasia has been adequately documented, by immunocytochemical counts of gastrin cells in the resected antrum. The patients had preoperatively basal gastrin levels in pg/ml A 180, B 170, C 92 respectively and after
food response A>800, B>800, C 390. Se-gastrin levels were similar after vagotomy and were eliminated after precise antrectomy. In all patients gastrin cells were found three to four times more per field of vision than normal.

As a conclusion we believe that antral G-cell hyperplasia is a definite clinical entity, characterised by recurrent peptic ulceration, hypertrophic gastric mucosal folds, and postprandial hypergastrinaemia, not necessarily associated with very high gastric acidity. We also believe that these patients can be identified at present by means of food-stimulated gastrin secretory studies.

F17 Smoking and peptic ulceration: an outpatient endoscopic survey

C C AINLEY, L C FORGACS, P W N KEELING, AND R P H THOMPSON (The Gastrointestinal Laboratory, The Rayne Institute, St Thomas’ Hospital, London) The relationship of smoking to peptic ulceration is controversial. Epidemiological surveys suggest an association, but these have rarely been based on endoscopy. We have therefore studied the smoking histories of patients attending for outpatient endoscopy.

The endoscopy unit at St Thomas’ Hospital provides a service open to all hospital doctors and local general practitioners. Between April 1981 and March 1982 all patients attending for outpatient endoscopy completed a questionnaire on their smoking history and were interviewed; 1217 patients over the age of 18 were studied 42 with carcinoma of the oesophagus or stomach were excluded. Three hundred and four had never smoked regularly, 241 were ex-smokers, and 594 smokers. There was no difference in the incidence of benign gastric ulcer between never smoked regularly and ex-smokers, but there was a significantly increased incidence in smokers compared with both never smoked regularly (χ²=15-5, p<0-001) and ex-smokers (χ²=5-4, p<0-02). Similarly, in duodenal ulceration there was no difference between never smoked regularly and ex-smokers, but there was an increased incidence in smokers compared with never smoked regularly (χ²=12-2, p<0-001) and ex-smokers (χ²=6-9, p<0-01). In addition, there was a increased incidence of both gastric ulcer and duodenal ulceration with increasing cigarette consumption.

In conclusion, in patients having outpatient endoscopy there is an association between current smoking and both gastric and duodenal ulcers.

F18 Effects of smoking on gastric secretion: loss of inhibition by antisecretory drugs

E J S BOYD, J A WILSON, AND K G WORMSLY (Department of Therapeutics, Ninewells Hospital, Dundee) Smoking adversely affects healing and recurrence rates in patients with duodenal ulcers. We investigated the effects of smoking on pentagastrin-stimulated and overnight basal gastric secretion in patients receiving antisecretory drugs. Six habitual smokers underwent three tests. After an overnight fast gastric secretion was stimulated by a submaximal dose of pentagastrin (0-5 mg/kg/h). Gastric juice was collected for 6×15 minute periods, volumes noted, and aliquots assayed for pH, H⁺, and pepsin.

On two of the days the subjects received cimetidine 200 mg orally 60 minutes before gastric intubation. On one of the days on which cimetidine was given subjects smoked cigarettes at a rate they found comfortable. Four of the subjects also had two further studies in which poldine 4 mg was given 60 minutes before the study.

Eleven patients being treated for duodenal ulcer had two tests on separate days. They took their evening dose of antisecretory drug (ranitidine 150 mg in five, cimetidine 400 mg in three, and LM24056 200 mg in three) at 18-00 h and gastric juice was collected from 20-00 h until 08-00 the next morning. On one of the nights they were allowed to smoke cigarettes ad libitum.

Inhibition of pentagastrin-stimulated secretion was not affected by smoking (acid (X±SEM) mmol/90 min – control 43±7, cimetidine 20±3, cimetidine + cigarettes 18±4, poldine 34±9, poldine + cigarettes 35±6; pepsin mg/90 minutes – control 208±36, cimetidine 93±15, cimetidine + cigarettes 91±17, poldine 148±31, poldine + cigarettes 156±24). Ten of the 11 patients showed increases in gastric acid and pepsin secretion on smoking during the overnight studies. Acid increased by a mean of 92% (from 25±8 mmol/12 h to 48±7 mmol/12 h p<0-02) and pepsin by 59% (from 446±89 mg/12 h to 709±63 mg/12 h p<0-05).

Smoking can markedly decrease the inhibitory effects of antisecretory drugs on basal gastric secretion. This may contribute to the poor therapeutic response in patients with duodenal ulcer who smoke.

F19 Luminal pancreatic enzymes: aspects of their fate and function

E J S BOYD, J G R CUMING, A CUSCHIERI, AND K G WORMSLY (Department of Therapeutics, Ninewells Hospital, Dundee) It has been proposed that pancreatic enzymes in the upper small intestinal lumen can modulate pancreatic secretion by inhibition of CCK release, and that up to 92% of luminal pancreatic enzymes may be reabsorbed intact and recirculated to the pancreas as part of an enteropancreatic conservation mechanism. We studied changes in serum immunoreactive trypsin after intraduodenal loads of endogenous trypsin, and, also, the effects of oral pancreatic enzyme supplements on pancreatic fistula output of enzymes.

Eleven patients had complete collection of duodenal contents during stimulation of pancreatic secretion by secretin (1 CU kg h) and CCK (1 IDU kg h) for 45 minutes. Five patients had a repeat test on a separate day in which duodenal contents were sampled (5 ml/15 minutes) instead of being completely aspirated. In six patients pancreatic juice collected during the 45 minute period of stimulation was rapidly reinfused into the duodenum at the end of the period of aspiration serum immunoreactive trypsin was measured in all subjects before stimulation with secretin-CCK and after 20 and 45 minutes of the hormone infusion. Serum immunoreactive trypsin was also measured after 60, 75, and 90 minutes in those subjects in whom duodenal juice was reinfused.

Daily volumes, trypsin output and mean trypsin concentration were measured in three patients with pancreatic fistulae during control periods and while receiving oral pancreatic enzyme supplements (Pancrex V, 2 capsules two hourly).

Serum immunoreactive trypsin did not change during stimulation with secretin-CCK, nor did it increase when an endogenous trypsin load was provided by avoiding aspiration or reinfusion. Recirculation of large amounts of trypsin is therefore unlikely. Evocative tests of pancreatic function based on serum immunoreactive trypsin are not likely to be of diagnostic value. Enzyme supplements consistently reduced mean trypsin concentration and trypsin output and there was a
rebound on stopping. This supports the theory that luminal enzymes can inhibit pancreatic secretion. Pancreatic enzyme supplements are useful in the management of pancreatic fistulae.

F20 Tubal pancreatic function testing with dual labelled cobalamin
J LEUNG, R FROST, H WATERS, J BRAGANZA, AND P B COTTON (Departments of Gastroenterology, The Middlesex Hospital, London, and Royal Infirmary, Manchester) The fact that some patients with chronic pancreatitis have abnormal Schilling tests led to proposals for a test of pancreatic function based on pancreatic enzyme separation of R protein from cobalamin before transfer to intrinsinc factor. We have assessed this system in 66 subjects. The fasting patient swallows a capsule containing 0.125 µg intrinsic factor (IF) bound Co57 cyanocobalamin, 0.125 µg (R) protein bound Co57 cyanocobalamin, and 125 µg cobaminide, and is given an intramuscular flushing dose of cyanocobalamin. The patient fasts for another two hours. Urine is collected for 24 hours. An aliquot is counted, and the relative absorption of R-Co57 cobalamin and IF-Co57 cobalamin calculated.

In 10 normal subjects, the mean ratio was 0.75 (95% reference range 0.52-0.99), 16 non-pancreatic gastrointestinal diseases 0.79 (0.48-1.09), 21 chronic pancreatitis (CP) 0.56 (0.1-1.11), eight pancreatic cancers (CA) 0.43 (0.9-0.93), and 11 recurrent acute pancreatitis 0.84 (0.63-1.03). The sensitivity for chronic pancreatic diseases (CP + CA) was 48% and the specificity for non-pancreatic disease was 87-5%. In recurrent acute pancreatitis, all tests were normal. There were 13 patients with steatorrhoea; two with small bowel cause had results within the normal range, whereas seven (three (CA + four CP) of the 11 with pancreatic steatorrhoea had abnormal results. Abnormal results were found in only four of 12 patients with pancreatic calcification. The test is simple to perform, and irradiation dose is low (0.5 mR—50 mR). Further assessment is justified.

F21 Atropine suppression of pancreatic polypeptide (PP) completely distinguishes tumour PP production from other rises
T E ADRIAN, S M WOOD, AND S R BLOOM (Department of Medicine, Royal Postgraduate Medical School, London) To date there have been few genuine routine clinical applications of the measurement of gut hormones. We have run a weekly pancreatic endocrine tumour screen for several years. A common problem is moderate rise in plasma PP concentrations which may be due to an apudoma or, alternatively, to a variety of other causes—for example, diabetes, renal impairment, infections, stress, chronic alcohol abuse, or old age. As normally PP release is dependent on the cholinergic innervation, it has been suggested that atropine administration should distinguish between autonomous PP secretion by tumours and normal PP release, which is always suppressible by atropine. The effect of atropine (1 mg, intramuscularly) on plasma PP concentrations was investigated in 12 patients with producing pancreatic endocrine tumours (two insulinomas, three gastrinomas, one glucagonoma, one VIPoma, and five PPomas). After atropine there was no significant change in circulating PP concentrations (median basal PP level 2050 pmol/l, range 440—30,000). Thus at 15 minutes PP was 107±4% of basal (mean±SEM) at 30 minutes 99±4%, and at 60 minutes 102±6%. In contrast, all subjects in control groups showed a large fall (p<0.005). These findings suggest that tumour-produced PP is unaffected by cholinergic blockade. The 'atropine test' with two key blood samples (zero and 30 minutes) may greatly help to detect early, and treatable, tumours in those patients who have an intermediate rise of plasma PP.

F22 Neodymium YAG laser photocoagulation for major acute upper gastrointestinal haemorrhage
I A MACLEOD, P R MILLS, J F MACKENZIE, R I RUSSELL, AND D C CARTER (University Department of Surgery and Gastroenterology Unit, Royal Infirmary, Glasgow) A prospective single blind controlled study was started in October 1980 to evaluate the neodymium YAG laser in the management of major haemorrhage from peptic ulcers and single vessels. Entry was restricted to patients with major blood loss as judged by clinical (shock, haemoglobin <10 g/ml, and need for blood transfusion) and endoscopic (arteries or red and black spots in ulcer base) criteria. Patients were assigned randomly to laser or sham therapy and the incidence of further haemorrhage and need for emergency surgery assessed by independent observers.

Six hundred and fifty-seven patients were admitted with acute non-varical upper gastrointestinal bleeding of whom 184 were bleeding from peptic ulcers or single vessels; 130 of these failed to fulfil the entry criteria and all settled on conservative management. Fifty-four patients were eligible for the study and 45 were included. Twenty patients bled from arteries: only one of eight who received laser therapy required emergency surgery and survived, whereas all eight receiving sham therapy needed emergency surgery and two died. Four patients allocated to laser therapy did not receive it for technical reasons. Twenty-five patients were bleeding from red/black spots and all settled irrespective of therapy.

A group of patients at high risk of recurrent haemorrhage can be identified. Laser therapy reduces the incidence of further haemorrhage and need for emergency surgery in patients bleeding from arteries.

F23 N-nitrosocompounds after operation for duodenal ulcer
M R B KEIGHLEY, D MORRIS, V POXON, D YOUNGS, D W BURDON, T J MUSCROFT, J BARNARD, P M G BAVIN, R W BRIMBLECOMBE, D W DARRK, P J MOORE, AND N VINCE (The General Hospital, Birmingham, and Smith Kline & French Research Limited, Welwyn, Herts). There is some evidence that there is an increased risk of gastric carcinoma after resection or vagotomy for duodenal ulcer. N-nitrosocompounds are powerful carcinogens which may be formed in the hypochlorhydric stomach. Analysis of nitrosamines from fasting gastric juice were reported to be high after partial gastrectomy but not after vagotomy. We have analysed half-hourly gastric samples for pH, nitrite, total, and stable N-nitrosocompounds from four groups over 24 hours taking a standard diet: proximal gastric vagotomy (PGV n=7), truncal vagotomy and pyloroplasty (TVP n=7), truncal vagotomy and antrectomy (TVAn n=8), and controls (n=8). Statistical comparison of groups was performed by calculating the area under the curve per hour (auc/h) for individuals by analysis of variance.
pH was significantly higher after TVA (auc/h = 4.67) than after TVP (auc/h = 2.52), PGV (auc/h = 4.94), and control (auc/h = 2.21) (p < 0.001). Nitrite values increased with pH and were significantly higher after TVA than control (p < 0.01). By contrast, neither total nor stable N-nitrosocompounds increased with pH and there was no significant difference in total N-nitrosocompounds between the groups.

If gastric carcinoma is more common after operation for duodenal ulcer it is unlikely to be due to intragastric nitrosation.

F24
New radioimmunoassay for cholecystokinin (CCK): relationship between post-prandial CCK levels and gall bladder (GB) contraction

I C Forgacs, M N Maisey, G M Murphy, and R H Dowling (Department of Medicine, Guy’s Hospital and Medical School, London) Although the pharmacological effects of cholecystokinin are well established, little is known about the physiological role of circulating cholecystokinin in contracting the gall bladder — mainly because its RIA is notoriously difficult, as antisera to cholecystokinin often lack specificity and conventional radiolabelling reduces cholecystokinin immunoreactivity. We therefore used an iodination technique, which avoids oxidative damage to the peptide, and raised several anti-cholecystokinin antisera, one of which cross-reacted equally with CCK₄ and CCK₃₃ but not with gastrin, and in six controls and seven patients with radiolucent gall stones measured fasting and post-prandial (Lundh meal) plasma cholecystokinin levels during studies of gall bladder emptying assessed both by ⁹⁹⁵ Tc-HIDA scanning and real-time ultrasound.

Results showed that fasting cholecystokinin levels were below the lower limit of assay detection (2 pmol/l) but 15 minutes after the meal, rose to 33.8 ± 5.8 in controls and 37.2 ± 5.3 in the patients, the 0–60 minute post-prandial profiles being comparable in both groups. Gall bladder contraction, however, was markedly different, the t½ emptying (HIDA scan) being 10±2 ± 1 minutes in controls and 21.7 ± 3.1 in gall stone patients. A similar pattern of results was seen with ultrasound, the reduction in gall bladder volume after the meal being greater in controls (14.8 ± 2.5 ml) than in gall stone patients (9.1 ± 1.8; p < 0.05).

To summarise: (1) a sensitive and specific RIA for plasma cholecystokinin has been developed; (2) post-prandial cholecystokinin release was comparable in gall stone patients and in controls; while (3) gall bladder emptying, studied by two separate methods, was reduced in gall stone patients suggesting that gall bladder end-organ response to endogenous cholecystokinin is altered in gall stone patients.

F25
Is percutaneous functional cholecystectomy feasible?: an experimental study in the rabbit

T V Taylor, D French, and I Cappeauld (Manchester Royal Infirmary and Ethicon Research Laboratories, Edinburgh) For the elderly, frail, unfit patient with gall stones, drug therapy takes months to become effective, is expensive, and on stopping treatment the stones rapidly recur. The present study was performed to assess the feasibility of defunctioning the gall bladder by occluding its lumen with Ethibloc. On hydration this substance undergoes rapid physical change from a viscous liquid to a solid similar to ‘sponge rubber’.

When injected subcutaneously into the rat Ethibloc became encapsulated with no effect on the bolus. Twenty-five rabbits underwent aspiration of their gall bladder contents, which were replaced by Ethibloc. Groups of five animals were killed at seven, 14, 28, and 182 days. Control animals underwent cystic duct ligation.

Up to 28 days from the time of injection, Ethibloc remained in the gall bladder unchanged, occluding the lumen and producing minimal inflammatory change. At six months partial resorption of the substance had occurred in some animals. No gall stones or cholesterol deposits developed in the gall bladder and none of the substance could be detected in the common bile duct. No infection occurred and liver function tests remained normal throughout the study. The implications of these findings are discussed in the light of performing percutaneous ‘functional cholecystectomy’ under ultrasound control.

F26
Retained common bile duct stones: mono-octanoin or endoscopic sphincterotomy?

J Dawson and R Cockel (Selly Oak Hospital, Birmingham) The increasing recognition of retained common bile duct stones as a cause of post-cholecystectomy symptoms necessitates constant evaluation of the optimum mode of therapy. Endoscopic sphincterotomy is now regarded by many as the treatment of choice but carries a definite morbidity and mortality. Mono-octanoin has recently been reported to successfully dissolve stones in selected patients but has not been evaluated in conjunction with sphincterotomy. In this study we have evaluated the alternatives of endoscopic sphincterotomy and monooctanoin infusion in 41 consecutive patients with retained stones presenting to a District Hospital.

Mono-octanoin infusion completely dissolved stones in seven of 12 patients with T-tubes in situ. In five patients with large stones mono-octanoin, infused through a nasobiliary cannula, dissolved stones in two and markedly reduced the size of stone in a further patient. In 29 of 32 patients with residual stones complete removal was achieved by endoscopic sphincterotomy. There were no complications of mono-octanoin therapy, but endoscopic sphincterotomy was complicated by haemorrhage in two patients and pancreatitis in one.

Thus mono-octanoin is a safe first line agent for dissolving retained stones in selected patients, while the remainder can be effectively treated by endoscopic sphincterotomy without recourse to surgery.

F27
Gall stones and mortality: a post mortem study of gall stone-related deaths

T Bates, P J Godfrey, M Harrison, M B King, and N R Padley (William Harvey Hospital, Ashford, Kent) In a prospective study of gall stones, all post mortem reports and death certificates issued in a Health District were scanned over a 2 year period. The prevalence of gall stones at necropsy was 17% but of these subjects only 11% had had a cholecystectomy.

During the period of study, 391 cholecystectomies were carried out in the District of which 73% were in women. There were 10 deaths in the necropsy series of 1701, directly related to gall stone disease, of which five were postoperative (1.3% operative mortality). Eleven further deaths were considered to have been due to gall stones in the 6356 subjects who did not have a necropsy. Cholelithiasis...
was found at necropsy in 19 of those with gall stones (6-5%) and was responsible for two deaths.

Gall stones have been reported as having a negative correlation with coronary heart disease and a positive one with certain forms of cancer. The age-sex corrected prevalence of coronary heart disease and cancer, however, was similar in those subjects with gall stones and those without. Carcinoma of the gall bladder was noted in one woman with gall stones but carcinoma of the caecum was not found in any of the post-cholecystectomy subjects.

It is concluded that, although gall stones are common, most remain unoperated and the mortality is low. The relationship to heart disease and cancer is still uncertain.

F28 Inhibition of gastric acid secretion in Zollinger-Ellison syndrome by omeprazole, a potent and long-acting antisecretory drug

C B H W LAMERS AND J B M J JANSEN (Division of Gastroenterology, St Radboud Hospital, Nijmegen, The Netherlands) The efficacy of histamine H₂-receptor blocking agents in patients with Zollinger-Ellison syndrome is limited by the short duration of acid inhibition. It has been shown that omeprazole (Hässle, Sweden), a substituted benzimidazole, inhibits pentagastrin stimulated gastric acid secretion in normal subjects for at least 48 hours. We therefore studied the effect of a single oral dose of 80 mg omeprazole on gastric acid secretion in six patients with Zollinger-Ellison syndrome (four men, two women, aged 31–51 years). All had hypergastrinaemia (serum gastrin 440–6475 pg/ml) with a positive secretin provocation test and gastric acid hypersecretion (BAO 13.3–90.8 mmol/h). In the second hour after ingestion of the drug gastric acid secretion was inhibited by 98±2%. Five patients were achlorhydric, while one patient, having the lowest plasma omeprazole concentrations, had 90% inhibition of gastric acid. At 24 hours after ingestion of the drug gastric acid was inhibited by 83±6% (56–100%). At that time omeprazole was undetectable in plasma from four patients, while the omeprazole concentrations were very low in the two other patients with Zollinger-Ellison syndrome. Clinical symptoms (diarrhoea in five, gastric discomfort in two, heartburn in two) were completely abolished for at least 48 hours. Serum gastrin concentrations were not influenced by omeprazole. No side-effects or laboratory abnormalities were induced by the drug.

We conclude that omeprazole is a potent and long-acting antisecretory drug in patients with Zollinger-Ellison syndrome.

F29 Identification of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) isoenzymes in patients with alcoholic liver disease

J B SAUNDERS, B R RICCIARDI, D A HOPKINSON, AND R WILLIAMS (The Liver Unit, King’s College Hospital and Medical School, London) Variations in the isoenzyme composition of ADH and ALDH underly certain acute effects of alcohol such as facial flushing. The relationship between the isoenzyme components and the chronic toxic effects of alcohol has not yet been established. We have developed a method for simultaneous analysis of ADH and ALDH isoenzymes by starch gel electrophoresis in 2.5 mg liver biopsy samples, and have investigated their phenotypes and relative activities in 65 patients with alcoholic liver disease (28 with fatty liver, 12 with alcoholic hepatitis, and 25 with cirrhosis).

Isoenzymes coded by the four ADH loci were identified in all biopsy samples. The phenotype frequencies of the isoenzymes coded by ADH₁ and ADH₂ loci were similar in the three histological groups and also comparable with those in the general population. Overall ADH activity and the relative activities of the individual isoenzymes were also similar in the three groups.

Up to five distinct isoenzymes of ALDH were seen. In all patients the fast-migrating mitochondrial band was present, indicating the 'usual' ALDH phenotype. In patients with alcoholic cirrhosis there was a selective reduction in staining intensity of this component (mean score 2.6 compared with 3.7 and 4.0 for patients with fatty liver and alcoholic hepatitis respectively, p<0.025). Other components were relatively weaker and there were no significant differences in mean scores between patients in the three histological groups. Selective reduction in the mitochondrial component of ALDH in alcoholic cirrhotics, by limiting oxidation of acetaldehyde, could be an important factor potentiating liver damage.

F30 Hepatoma-specific alkaline phosphatase (H-ALP) in high and low incidence areas of primary liver cancer

P KAY, P J JOHNSON, T W WARNES, R WILLIAMS, M LONGSON, I LAING, A SMITH, AND N W LEE (University Department of Gastroenterology, Manchester Royal Infirmary, Manchester; The Liver Unit, King’s College Hospital, London; and the Department of Surgery, Queen Mary Hospital, Hong Kong) We wished to compare the diagnostic value of H-ALP and α-fetoprotein (AFP) in primary liver cancer in Hong Kong, an area of high incidence with high carriage rates of the hepatitis B virus (HBV) and in the United Kingdom, an area of low incidence with low carriage rates of HBV.

Forty-four Chinese and 87 Caucasian patients with primary liver cancer were studied. ALP isoenzymes were demonstrated by polyacrylamide gel electrophoresis. AFP was measured by radioimmunoassay and HBSAg by passive haemagglutination inhibition and radioimmunoassay.

Results showed that, although the incidence of raised AFP was the same in the two groups, the serum AFP levels were much higher in the Chinese than in the Caucasians (1.4×10⁶ ng/ml compared with 7.8×10⁵ ng/ml, p<0.001). The incidence of the HBSAg was 74% in the Chinese and 18% in the Caucasians (p<0.001). The incidence of H-ALP in the Chinese was only 2% compared with 18% in Caucasians (p<0.05). In the Caucasian group, patients with cirrhosis had a higher incidence of raised AFP than non-cirrhotics (p<0.0005) and H-ALP was found in 29% of non-cirrhotics compared with only 10% of cirrhotics (p<0.05).

We conclude that Chinese with primary liver cancer have high levels of AFP and HBSAg but a low incidence of H-ALP (2%). In Caucasians, the levels of AFP and incidence of HBSAg are lower but H-ALP is much more common (18%). Thus, the varying incidence of tumour markers may reflect biological differences in hepatoma found in high and low incidence areas of the world. H-ALP is of particular value in the diagnosis of primary liver cancer in Caucasian non-cirrhotics, in whom AFP levels are often normal.
F31 Prevention of perinatal transmission of hepatitis B by selective passive immunisation

R J Stocks, A E Flower, P Nuttall, and M S Tanner (introduced by Professor A S McNeish) (Department of Child Health and PHLS, Leicester Royal Infirmary and Regional Transfusion Centre, Sheffield) Chronic carriage of HBsAg confers a high risk of chronic liver disease and hepatoma, and frequently results from perinatal HBV infection from carrier mothers. The efficacy of selective passive immunisation of babies at risk is evaluated. Antenatal HBsAg positive sera are examined for HBeAg and anti-HBe. Babies of HBeAg positive mothers, and of mothers with perinatal acute hepatitis B, receive hepatitis B immune globulin 250 mg at birth, then monthly for six months. Anti-HBe positive mothers' babies are followed without HBIG. No attempt is made to sterilise the vagina, to wash out the baby's stomach, or to inhibit breast feeding.

Of 36 HBsAg-positive pregnancies, eight had HBeAg (four from SE Asia). Seven HBIG-treated infants, together with two HBIG-treated infants of mothers with acute hepatitis, were followed; none has developed HBsAg, and three have developed anti-HBe or anti-HBs in the second year. Twenty-eight mothers had anti-HBe, and none of their 18 babies followed has become an HBsAg carrier; one infant developed transient antigenaemia and raised transaminases at 3 months of age, subsequently developing anti-HBs and anti-HBe. Among older siblings of study infants, five chronic carriers of HBsAg and HBeAg were detected. We conclude that (1) anti-HBe positive pregnancies do not result in HBsAg carrier infants, but transient antigenaemia and subsequent active immunity may occur; (2) HBIG gives short-term protection in all and, by permitting active immunity to develop, long-term protection in some babies of HBeAg positive mothers. These data support the selective use of HBV vaccine when available.

F32 Nuclear magnetic resonance (NMR) imaging of the liver

S H Saverymuttu, H J F Hodgson, G M Bydder, and R E Steiner (Departments of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London) Nuclear magnetic resonance scans of the liver were obtained in 12 normal volunteers and 32 patients with biopsy proven liver diseases and the results compared with x-ray computer tomography. In addition to the visual images derived from nuclear magnetic resonance imaging, tissue proton longitudinal relaxation times (T1) were calculated in the different conditions.

Both methods demonstrated focal liver disease, but an extensive area of focal atrophy in one patient, and of hepatic infarction in another were detectable only by nuclear magnetic resonance. In diffuse liver disease, it showed a prolongation of T1 in cirrhosis but was not of diagnostic specificity. The images in three patients with cirrhosis were abnormal only with the nuclear magnetic resonance technique, and not by computer tomography. In contrast, in steatosis computer tomography images were virtually diagnostic, while nuclear magnetic resonance scans showed no specific features.

Initial results of nuclear magnetic resonance scanning as a non-invasive technique for investigating liver disease are promising, but more experience is required to evaluate its potential.

F33 Single photon emission tomography (SPET) in the evaluation of liver disease

A J Morris, M Roberts, M Critchley, and J S Grime (Gastro-Intestinal Unit, Walton Hospital, and Departments of Medicine and Nuclear Medicine, Royal Liverpool Hospital, Liverpool) Conventional isotope scans provide limited information about hepatic function because of failure to account for liver volume. Rather than searching for mass lesions within the liver, we have developed a technique using SPET to measure hepatic volume and uptake of radiopharmaceutical. Thirty patients with histologically proven liver disease were scanned with a GE 400T tomographic camera, 15 minutes after intravenous injection of 4mCi99mTc sulphur colloid. Transverse sections of the liver were reconstructed using SPET software, and liver volume derived using an edge detection programme.

The sensitivity in measuring isotope activity and accuracy of volume estimations were assessed using phantoms, and high degrees of correlation were found (sensitivity r=0.98, volume r=0.99). Reproducibility of liver volume estimations was ±3%. Patients with the most severe liver disease (decompensated cirrhosis) had lowest uptakes per injected dose of isotope 19%±6 (SD); those with inactive cirrhosis or clinically moderate chronic liver disease had uptakes of 41%±5, while patients with minimal hepatic dysfunction, either with normal biopsies or chronic persistent hepatitis, had the highest uptakes (57%±5).

The use of 99mTc sulphur colloid allowed sufficient time for the development of analytical techniques without interference from secretion into the gut. Despite specific uptake by Kupffer cells in the liver the results correlated well with clinical and histological assessments. Studies of more specific hepatocellular radiopharmaceuticals – for example, BSP – are continuing, as the method permits non-invasive longitudinal assessment of liver function.

F34 Propranolol for prevention of recurrent variceal bleeding in cirrhotic patients

R P Walt, A K Burroughs, A A Dunk, W J Jenkins, and S Sherlock (Royal Free Hospital School of Medicine, London) We report a controlled study of propranolol for the prevention of rebleeding in patients with cirrhosis.

Since June 1981 42 consecutive patients with cirrhosis, who had been admitted with bleeding oesophageal varices, were randomly allocated to propranolol or placebo treatment after their condition had stabilised. Propranolol was given to reduce the resting pulse by 25%. The two groups did not differ significantly in age, sex, cause of cirrhosis, or Child's grade.

Results showed that there was no significant difference in rebleeding, between the groups – seven in each (p 0.90), all from oesophageal varices. There were three deaths, all from recurrent variceal haemorrhage – two in the propranolol group and one in the placebo group.

These results contrast with those of a previous study of mainly alcoholic patients in good condition, in which propranolol did reduce recurrent gastrointestinal bleeding. Our patients were unselected, so that both the aetiology of the cirrhosis and the
severity of the liver damage varied, but they were representative of the population at risk of rebleeding. Propranolol not only failed to prevent rebleeding, but the β-blockade seriously complicated the resuscitation of two patients who bled.

F35
Controlled trial of high and low dose D-penicillamine (DP) in primary biliary cirrhosis (PBC): results at three years

M F BASSENDINE, A F MACKLON, R MULCAHY, AND O F W JAMES (Department of Medicine, University of Newcastle upon Tyne, Newcastle upon Tyne) Fifty-nine consecutive patients with primary biliary cirrhosis were randomly allocated to one of three groups – 19 received 1 g DP daily, 21 received 250 mg DP daily, 19 controls received no DP. The groups were comparable with respect to age, symptoms, disease duration, LFTs and histological stage. Mean period of follow-up was 37 months, minimum follow-up in survivors was 29 months. Changes in bilirubin, AST, alkaline phosphatase, albumin, IgG, IgM, and antimitochondrial antibody titre were analysed at six-monthly intervals.

The following achieved statistical significance (p<0.05). High dose vs control: AST lower at six, 12, and 30 months, IgM lower at six, 12, and 30 months, IgG lower at 12, 18, 24, and 30 months. Low dose vs control: AST lower at six and 12 months, IgG lower at 12 months, alkaline phosphatase lower at 24 months. No other measurement showed significant change in either group at any stage.

Mortality: high dose 2/19 (deaths at five and 20 months), low dose 8/21 (six liver related, four of whom received <18 months DP), controls 2/19. Eleven of 12 patients who died had cirrhosis on entry to trial. Side effects occurred in 14 (35%) – nine high dose, five low dose; these required withdrawal of drug in nine (23%).

We conclude that (1) in high dose, while DP produced a consistent improvement in AST and immunoglobulins, no significant change occurred in bilirubin nor histological stage, nor was mortality influenced; (2) in low dose transient improvement only was seen in AST and immunoglobulins. It is possible that these limited changes indicate that higher dose DP over many years could benefit those patients able to tolerate the drug.

F36
Species differences in copper toxicity and their relevance to Indian childhood cirrhosis (ICC)

A KANTARJIAN, A GHOSH, AND M S TANNER (introduced by Professor A S McNish) (Department of Child Health, University of Leicester, Leicester) Cu-supplemented lambs and rats were studied as animal models of Indian childhood cirrhosis. Groups of five male lambs received 0, 1, 2-5, and 5 mg/kg/day Cu for 13 weeks. Liver Cu in percutaneous biopsies rose from 199±96 µg/g to 930±60, 1810±340, and 1720±100 µg/g at four weeks; 1770±220, 3200±450, and 2980±320 µg/g at eight weeks. Lambs thrived initially, with normal serum δGT, copper + caeruloplasmin values, but at eight to 12 weeks rapidly deteriorated with jaundice, rising δGT, haemolysis, and methaemoglobinaemia. Rats differed in five respects: (1) pretreatment liver Cu was lower (27±14 µg/g); (2) a higher Cu dose was required; 3 mg/kg/day was ineffective, but Cu supplementation of drinking water to supply 20 and 40 mg/kg/day for 10 weeks increased liver Cu to 316±230 µg/g and 562±424 µg/g; (3) no haemolytic crisis occurred; AST was raised to twice normal at four weeks and 4× normal at eight weeks; (4) whereas Cu-loaded lamb biopsies showed heavy rhodanine, Timm's, and orcin staining, rat biopsies with comparable Cu concentrations measured biochemically were orcin negative; (5) ultrastructurally, lamb biopsies contained numerous electron-dense lysosomes, shown by electron probe analysis to contain Cu and S, while rat lysosomes were much less electron-dense and contained scanty Cu and S.

Species differences in physiological hepatic Cu concentration, in its lysosomal aggregation, in orcin-demonstrable Cu-binding proteins, and in susceptibility to Cu-toxicosis, are important constraints on extrapolating animal data to man.

F37
Is intrahepatic cholestasis in sickle haemoglobinopathies a benign condition?

S I TERRY, B HANCHARD, AND G R SERJEANT (Departments of Medicine, Pathology and MRC Laboratories, University of the West Indies, Mona, Kingston 7, Jamaica, WI) Intrahepatic cholestasis in sickle haemoglobinopathies (IHSS) is said to carry a high mortality. Experience in 16 patients with IHSS admitted to the University Hospital of the West Indies suggests a more benign prognosis. Fifteen had SS disease and one SD Punjab (11 males and five females) with ages ranging from 8 to 42 years (mean 20 years). The diagnosis of IHSS was based on rapidly deepening jaundice, cholestatic features, absence of large duct obstruction, and a liver biopsy with typical changes as described below. Clinical features included a prodrome with or without fever (12), dark urine (16), and soft, smooth hepatomegaly (13). None had evidence of liver failure. Previous episodes of IHSS had occurred in five. Serum bilirubin and liver enzymes were raised, whereas serum albumin and prothrombin time were normal. Haemoglobin levels and reticuloocyte counts did not differ from the steady state. Liver biopsy revealed normal liver architecture without hepatocellular necrosis, intrahepatic bile pigment, and congestion of the sinusoids by sickled erythrocytes in all cases. Ultrastructural examination of the liver, performed in 12, showed mitochondrial elongation or granulation in seven. Resolution occurred in all, within two weeks in 15. Although the outcome of IHSS in our patients appeared benign, monitoring of such episodes in hospital is considered advisable.

F38
Prospective study of jaundice after cardiopulmonary bypass surgery

J COLLINS, M F BASSENDINE, R FERNER, A MURRAY, AND O F W JAMES (Departments of Medicine and Medical Physics, Freeman Hospital, Newcastle upon Tyne) We studied 248 patients undergoing cardiopulmonary bypass surgery to determine the incidence and possible causes of early 'postpump' jaundice. Factors suggested by previous retrospective studies to be associated with this type of jaundice, were examined prospectively; preoperative LFTs, peroperative minimum mean arterial blood pressure (mMAP), PaO₂, bypass time, oesophageal temperature, and type of operation. Alcohol intake, drugs and anaesthetics, blood transfused, postoperative blood pressure and PaO₂ were also recorded. LFTs and tests for haemolysis were measured postoperatively on alternate days. Postpump jaundice (bilirubin ≥50 µmol/l) occurred in 49 patients (20%); this was detectable in 48/49 by postoperative day 2, when the bilirubin
was over 75% conjugated; in 44/49 bilirubin began to fall by postoperative day 6; early postoperative ALT was normal. Hepatic alkaline phosphatase did not rise until after day 6, the rise often being prolonged. Bilirubin was slightly raised postoperatively (18-49 μmol/l) in a further 140 subjects (56%). Fourteen of 248 patients died; of these 12 were in the postpump jaundice group (p<0.0005). At necropsy liver biopsy in seven showed only changes of chronic venous congestion. Postpump jaundice patients received more blood (10±7.6 units vs 5.3±3.6, p<0.01), and had longer bypass times (103±35 minutes vs 89±30, p<0.01) than those without postpump jaundice. Postpump jaundice developed after mitral valve surgery in 32/93 patients (p<0.0005). Contrary to previous hypotheses there was no association of postpump jaundice with mMAP, PaO₂, or haemolysis. No other factors were related.

We conclude that the incidence of postpump jaundice is high (20%) and carries a bad prognosis (12/49 died). It is an early conjugated hyperbilirubinaemia not associated with other evidence of liver cell damage or cholestasis, not explained by hypoxia, hypotension, or haemolysis.

F39
Endoscopic retrograde cholangio pancreatography (ERCP) in primary biliary cirrhosis
I HAMILTON, D J LINTOTT, W S J RUDDELL, AND A T R AXON (Gastroenterology Unit and Department of Diagnostic Radiology, General Infirmary at Leeds, Leeds) We have compared the endoscopic retrograde cholangiogram and pancreatogram of 22 unselected consecutively investigated patients with primary biliary cirrhosis with those of 33 patients with other forms of intrahepatic disease (‘control patients’) and 28 controls with normal pancreatic and biliary duct systems and no evidence of liver disease (‘normal subjects’).

The pancreatic duct was opacified in 17 primary biliary cirrhosis patients and was abnormal in only one; of the 29 control patients in whom a pancreatogram was obtained there were changes of chronic pancreatitis in eight. These changes were particularly frequent in seven patients with sclerosing cholangitis, of whom three had chronic pancreatitis.

The bile duct was opacified in 19 primary biliary cirrhosis patients and 28 control patients. The intrahepatic cholangiogram showed calibre variation and irregularity in seven primary biliary cirrhosis patients, 15 control patients, and one of the normal controls (p<0.05). There was a smooth, localised indentation of the common hepatic duct at the porta hepatis in 11 patients with primary biliary cirrhosis, and in none of the control patients or normal controls (p<0.05). It was not possible to correlate the presence of this indentation with the histological stage of the disease, but it was present in nine of the 12 patients with a normal intrahepatic cholangiogram and in only two of the seven with radiological features of cirrhosis (p<0.05). In three such patients undergoing laparotomy enlarged hilar lymph nodes were present, and may have been compressing the bile duct.

While the presence of this radiological abnormality has been described in a small proportion of patients with primary biliary cirrhosis its frequency has not been previously established. The presence of a smooth ‘notch’ on the extrahepatic cholangiogram is highly suggestive of primary biliary cirrhosis as distinct from other forms of intrahepatic disease.

F40
Gall bladder abnormalities in acute hepatitis: a prospective study
D P MAUDGAL, A E A JOSEPH, AND M H WANSBROUGH-JONES (Departments of Communicable Diseases and Nuclear Medicine, St George’s Hospital and Medical School, London) Oedema and increased thickness of the gall bladder wall found in cholecytitis can now be precisely measured by ultrasonography. Patients with acute hepatitis do not have any clinical signs of cholecystitis, but increased thickness of gall bladder wall has been reported in some cases. The cause and progression of thickness of gall bladder wall is not known.

We have compared gall bladder wall thickness in 22 healthy volunteers and 20 patients presenting with acute hepatitis due to hepatitis A in nine; B in one; Epstein Barr virus in two; and non-A non-B in eight patients. Gall bladder wall measured 2.0±0.06 mm (mean ± SEM) in controls and 5.35±0.46 mm in patients (p<0.001). On repeat measurements after clinical and biochemical recovery from acute hepatitis in nine patients, gall bladder wall thickness decreased from 6.22±0.59 mm to 2.44±0.29 mm (p<0.001). In seven patients the gall bladder contents gave an echogenic pattern suggestive of sludge, which cleared during recovery phase. Serum alanine transaminase was raised up to 2932 IU/l (normal <35 IU/l) and serum albumin ranged from 22 to 44 g/l (normal range 35–50 g/l). Gall bladder wall thickness significantly correlated with serum transaminase (r=0.65; p<0.001) and albumin levels (r=−0.49; p<0.001).

We conclude that local inflammation and hypoalbuminaemia might contribute to the increased thickness of gall bladder wall during acute hepatitis, and gall bladder returns to normal after complete recovery from hepatitis.

F41
Detergency of the bile acid (BA) pool determines biliary cholesterol (XOL) secretion and saturation in man
P LORIA, M BERTOLOTTI, R IORI, G TADDIA, M PONZ DE LEON, AND N CARULLI (Istituto di Clinica Medica II, Università di Modena – Divisione di Chirurgia, Ospedale di Castelfranco, Modena, Italy) It has been suggested that cholesterol secretion into bile might be dependent on detergent power of the bile acid pool. To test this hypothesis we investigated the effect of bile acid having different detergent capacity: deoxycholic acid (DCA), chenodeoxycholic (CDCA), cholic (CA), and ursodeoxycholic (UDCA), in decreasing order on bile lipid secretion in man.

Six T-tube patients operated for cholecodolithiasis were studied. Each patient underwent two studies: three patients received CA and CDCA and three UDCA and DCA at three days’ interval. At the beginning of the study the enterohepatic circulation was interrupted via an occlusive balloon placed in the distal arm of the T-tube and bile was drained for five hours (pretreatment period); intraduodenal infusion of bile acid was then started at the rate of 1 g/h for five hours (replacement period). Bile samples were collected hourly throughout the study. Parameters investigated included bile flow, bile lipid output, and bile acid composition.

During the pretreatment period bile acid output was the lowest and only primary bile acids were present. In the replacement period the administered bile acid constituted 80–90% of the pool.

We conclude that at low bile acid output (pretreatment period), XOL/BA ratio and saturation index are the highest. In the bile acid stimulated bile lipid secretion, XOL output seems to be significantly related to the detergent power of the infused bile acid.
(DCA > CDCA > CA > UDCA). Our results support the hypothesis that a determinant of cholesterol secretion and saturation index is the detergency of bile acid pool.

F42
Effects of the vasoactive substance cyclandelate on hepatic HMGCoA reductase activity in rats and on biliary lipid composition in gall stone patients

B H WHITTEN, B MIDDLETON, A MIDDLETON, A MICIAK, D A WHITE, K W SOMERVILLE, AND G D BELL (Department of Therapeutics and Department of Biochemistry, University of Nottingham, Nottingham) Cyclandelate is a vasoactive substance (Cyclospasmol Gist-Brocades) consisting of the mandelic acid ester of 3,3,5-trimethylcyclohexanol (TMC). TMC is structurally similar to menthol (2-isopropyl-5-methyl-cyclohexanol) one of a group of cyclic monoterpene that we have shown to decrease hepatic cholesterol synthesis in rats and man by their inhibition of HMGCoA reductase activity in vivo. Hepatic HMGCoA reductase activity was measured in Wistar rats given one of the following: (1) TMC, (2) cyclandelate dissolved in olive oil, (3) olive oil alone, (4) mandelate in normal saline, or (5) normal saline alone. The TMC, cyclandelate, and mandelate were all given as a single dose of 6 mmol/kg. The rats were killed 17 hours later and the assays performed. Nine patients with radiotranslucent gall stones and radiologically functioning gall bladders had a bile sample taken by duodenal intubation after an overnight fast. They then took cyclandelate in a dose of 400 mg bds (3) or 800 mg bds (6) for a mean of 29 days before a second sample was obtained. A single dose of cyclandelate in the rats caused a 62% inhibition of HMGCoA reductase activity (p<0.01). The same degree of inhibition was obtained by TMC (p<0.01). Mandelate, the acid component of cyclandelate, gave no significant inhibition. The mean lithogenic index (H and D) of the gall stone patients fell significantly from 1.4±0.05 (mean ± SEM) to 1.1±0.07 (p<0.05) after cyclandelate. The improvement was due to a significant fall (p<0.05) in the molar ratio of cholesterol. Cyclandelate may prove to be a useful adjuvant to bile acid therapy, particularly in obese subjects with high hepatic HMGCoA reductase levels.

F43
Subcellular localisation of 125I intrinsic factor (IF) and 57Co cyanocobalamin (57CoB12) during absorption by guinea-pig ileum

H A SHEPHERD, J PRIDDE, W J JENKINS, AND D P JEWELL (Radcliffe Infirmary, Oxford) Previous studies have shown that a B12 is processed by the lysosomes and cytost during absorption through the ileal enterocyte. The fate of IF during B12 absorption is unknown.

Pure human 125I IF-57CoB12 complex prepared from a protein A anti IF column was applied to guinea-pig ileal tissue maintained in organ culture from 15 minutes to 2 hours. At selected time intervals, tissue was counted for gamma activity of both isotopes and homogenised. Subcellular organelles of the post nuclear supernatant (PNS) were fractionated on Percoll density gradients. The distribution of organelles was identified by enzyme markers and each fraction was counted for 57Co and 125I activity.

Both 125I and 57Co activity was detected in ileal tissue but only approximately 50% was removed after washing with 0-1M EDTA representing a net uptake of both isotopes. Subcellular fractionation at all time intervals demonstrated 125I and 57Co activity associated with the enzyme markers for brush border, lysosomes, and cysotol fractions. The lysosomal fractions were solubilised and run on Sephadex G150. 125I activity eluted in the range for IF and IF-B12 complex, whereas 57Co activity eluted in the range for the complex and free B12. No free 125I activity was detected. These results demonstrate that IF enters the cell during B12 absorption probably as the IF-B12 complex which is then processed by lysosomes.

F44
Effect of pectin on jejunal glucose absorption in man

B FLOURIE, N VIDON, C FLORENT, AND J J BERNIER (Inserm U54 – Hôpital Saint-Lazare, Paris, France) Ingestion of pectin improves glucose tolerance in both normal and diabetic patients. It has been shown that pectin delays gastric emptying, but a direct effect on intestinal glucose absorption has not been demonstrated so far in man, and experiments in rats gave conflicting results.

The acute effect of pectin on glucose absorption was studied by segmental perfusion technique with proximal occlusive balloon to eliminate the gastric factor. The effect of three different concentrations of pectin (6, 10, 15 g/l) was studied in 22 normal volunteers. Two solutions were infused (10 mg/ml) at the ligament of Treitz. They contained PEG (5 g/l), NaCl (130 mM), KCl (5 mM) with either glucose or manitol (30 mM). The length of the studied intestinal segment was 25 cm.

Results showed that, for each concentration of pectin, there was a significant reduction of water and sodium absorption (p<0.01), compared with either glucose or manitol control solutions. This reduction, however, was not dose-dependent. The absorption of 30 mM glucose was reduced by addition of pectin (p<0.01). This reduction of glucose absorption was dose dependent; mean percentages of inhibition on 25 cm segment were 10, 13, and 27%, respectively for 6, 10, and 15 g/l pectin, respectively (r=0.58, p<0.01). Pectin had no effect on glucose-linked sodium transport.

Our results show that, in healthy man, there is an acute inhibitory effect on intestinal glucose absorption. This effect is observed with low intraluminal pectin concentrations, similar to those achieved when pectin is given in a test meal.

F45
Studies of the mechanisms of action of the antidiarrhoeal agent loperamide

S HUGHES, N B HIGGS, AND L A TURNBERG (Department of Medicine, Hope Hospital (University of Manchester School of Medicine, Salford) Loperamide is an effective antidiarrhoeal agent with well-recognised effects on motility. We investigated the possibility that it might also influence intestinal absorption and have anti-secretory effects. Stripped rabbit ileal mucosa was mounted in a modified Ussing chamber. Loperamide (10-8 to 10-6M) added serosally caused a dose-related fall in potential different and short-circuit current (p<0.01) leaving resistance unchanged but was inactive on the mucosal side. This effect was inhibited by naloxone 10-4M (p<0.02). Loperamide 10-6M alone failed to influence basal ion transport but did inhibit secretion provoked by prostaglandin E2 (PGE2) and by E. coli heat labile toxin. Electrical responses to PGE2 (n=18) and E. coli (n=12) were not
A912

prevented by loperamide. The PGE₂ reduction in net Na absorption, however, (from 7-14±0-97 to 2.39±1-07, p<0.02, n=6) was partially inhibited by loperamide (7-16±0-88 to 5-47±0-82, n=6). PGE₂ induced net Cl secretion (from control of 1-89±0-70 to 1-2±0-99, p<0-01) was also inhibited (2-29±0-48 to 1-08±0-92 NS). Unidirectional flux responses were also inhibited.

Heat labile E. coli toxin (200 μl crude extract) reduced Na absorption (from 5-14±0-76 to 1-96±0-99, p<0-01, n=6) and induced Cl secretion (from 1-98±0-90 to 1-49±0-72, p<0-05, n=6) by reducing mucosa to serosa fluxes. Loperamide inhibited these responses (net Na absorption 4-25±1-04 to 3-46±1-43, NS and Cl, +1-74±1-06 to 0-32±0-83, NS). We conclude that loperamide influences intestinal mucosa through opiate receptors and part of its anti-diarrhoeal effect may be mediated by its anti-secretory activity.

F46
Can rapid small bowel transit limit absorption of a meal?

A N HOLGATE AND N W READ (Department of Physiology, University of Sheffield, Sheffield) The small bowel transit and absorption of radiolabelled solid meal of known composition were measured in 14 patients, who had had a terminal ileostomy fashioned for ulcerative colitis. Measurements were carried out under control conditions and after administration of three agents, which speeded up small bowel transit by different mechanisms. Small bowel transit time was taken as the difference between the half times for gastric emptying, measured by counting over the surface of the stomach with a crystal scintillation detector, and ileal emptying, measured by estimating the delivery of isotope from the stoma. The latter provided an excellent index of the delivery of fat, protein, and carbohydrate components of the meal (r=0-99). Absorption of the meal was determined by chemical analysis of the ileostomy effluent. Administration of either metoclopramide (20 mg tds), magnesium sulphate (7 g), or lactulose (40 g) significantly reduced small bowel transit time (p<0-05) and increased the weight of ileal effluent (p<0-05). All three agents significantly reduced the absorption of fat (p<0-05), and lactulose and magnesium sulphate also decreased the absorption of protein and carbohydrate (p<0-05).

We concluded that rapid small bowel transit may limit absorption by reducing the contact of food with the absorptive epithelium.

The British Society of Gastroenterology

F47
Adult hereditary fructose intolerance: isolation and characterisation of a mutant liver aldolase

T M COX, M W O'DONNELL, AND M CAMILLERI (Department of Medicine, Royal Postgraduate Medical School, London) Hereditary fructose intolerance (HFI) is a metabolic disorder caused by enzymic deficiency of aldolase B but the molecular basis of this defect is unknown. We have studied a remarkable family with hereditary fructose intolerance in a 45 year old man and his three children, all of whom had suffered typical abdominal pain, vomiting, and hypoglycaemic symptoms after fructose ingestion, since infancy. Assay of fructose-1-phosphate aldolase confirmed a profound deficiency (<2% control) of this specific enzyme activity in biopsy samples of liver and intestine. Moreover, kinetic studies showing a 10-fold mean increase in Michaelis constant (24–92 versus 1–6-3 mM) suggested the presence of an aberrant enzyme.

To characterise and isolate this putative mutant enzyme, immunochemical techniques were used: aldolase B was purified from human liver and monospecific anti-aldolase immunoglobulins were prepared from antisera raised in sheep. Immuno-diffusion gels showed a precipitin line common to the pure enzyme, normal liver, and intestinal extracts but reactions with other control tissues of hereditary fructose intolerance liver were not detected. A sensitive and specific radioimmunoassay was thus used to search for immuno-reactive aldolase (detection limit 7.5 ng; ID₅₀ 125 ng). Extracts of tissues from hereditary fructose intolerance patients gave 10–25% of control levels of immuno-reactive enzyme; immuno-reactive aldolase in four proven heterozygotes was, as expected, reduced (to 55%) when compared with seven control samples (p<0-05).

Immunooaffinity chromatography on anti-aldolase – Sepharose gels enabled pure aldolase to be recovered from liver supernatants. Electrophoresis in SDS-polyacrylamide showed a single protein band from hereditary fructose intolerance liver apparently identical with normal active aldolase (subunits 42600 daltons). In hereditary fructose intolerance there was a striking reduction in apparent specific activity of the aldolase and displacement immunotitration showed a markedly decreased affinity for antibody.

We conclude that aldolase B deficiency in hereditary fructose intolerance is associated with the synthesis of an immunoreactive but structurally altered enzyme protein.

F48
Improved methods for the metabolic profiling of bile acids in faeces

J M GILBERT, A M LAWSON, J WORTHINGTON, AND K D R SETCHELL (introduced by A G COX (Department of Surgery and Division of Clinical Chemistry, Clinical Research Centre, Harrow, Middlesex) Because of their probable role in the aetiology of diseases such as colon cancer and other gastrointestinal disorders, there has been renewed interest in the measurement of bile acids in faeces.

Improved techniques have been developed in our laboratory for the determination of metabolic profiles of faecal bile acids. These employ a combination of liquid-gel and liquid-solid extraction before group separation of bile acids according to their mode of conjugation. Metabolic profiles are obtained using high resolution capillary column gas chromatography with identification of compounds by mass spectrometry.

Twenty-seven different bile acids have been identified in the unconjugated state in the faeces of normal adult female Sprague-Dawley rats. Quantitative changes in the faecal excretion of these bile acids were studied over 14 consecutive days in two animals. Deoxycholic acid was the predominant bile acid excreted by both animals and ranged from 686-4545 μg/day. There was an abundance of 6-hydroxylated bile acids of which hyodeoxycholic was the most prevalent (491–3193 μg/day) and at least four muricholate isomers were identified. Contrary to previous reports, chenodeoxycholic and cholic acid were not present.

These data indicate that the metabolic profile is more complex than previously suggested. The methods provide increased sensitivity and specificity for investigation of the relationship between faecal bile acids and gastrointestinal diseases in humans and rats.
Reversibility of sucrase inhibition by acarbose in in vivo perfusion of the rat jejunum

R H TAYLOR and HELEN M BARKER (Department of Gastroenterology, Central Middlesex Hospital, London) The α-glucoside hydrolase inhibitor acarbose is a powerful competitive inhibitor of sucrase in man. An oral dose of 200 mg results in almost complete malabsorption of a sucrase load. In establishing a therapeutic dosage regime the kinetics of recovery of sucrase activity is important. In these experiments we have studied this in an in vivo perfusion model.

At laparotomy in five anaesthetised adult Sprague-Dawley rats a segment of proximal jejunum 20 cm long was cannulated and perfused in vivo with an isosmolar sucrose/saline solution. 14C PEG 4000 was used as an unabsorbable marker for calculation of absorption rates. Sugars in the aspirate were measured by high pressure liquid chromatography and electrolytes by flame photometry. After a half-hour stabilisation period, aspirates were collected at five minute intervals for three hours. In the second half-hour of the three hour period, acarbose 30 mg/l was also present in the perfusion solution.

Acarbose caused a rapid onset 86% inhibition of the sucrase absorption rate from 83.5±5.9 to 11.6±1.8 μmol/h/segment. There was a similar reduction in water and sodium absorption. Luminal fructose fell by 90% and glucose disappeared. Over the next two hours there was a gradual return of sucrase activity reaching 50% recovery after 75 minutes. A similar recovery in sodium and water absorption rates was seen.

The results show that acarbose is an effective reversible inhibitor of sucrase in the rat in vivo with half life of the order of 75 minutes.

F50
Hyperenteroglucagonaemia and small intestinal hyperplasia after colonic perfusion of glucose in the rat

R M MIAZZA, A FILALI, M A GHATEI, M Y T AL-MUKHTAR, N A WRIGHT, S R BLOOM, AND J C RAMBAUD (Inserm U54 – Hôpital Saint-Lazare, Paris, France; Departments of Medicine and Histopathology, Royal Postgraduate Medical School, London) Hormonal factors play an important role in intestinal adaptation and enteroglucagon is a strong candidate for the role of enteroendocrine. It is distributed throughout the intestine, with a maximal concentration in terminal ileum and colon. In most conditions associated with small bowel hyperplasia, such as lactation, enterectomy and pancreatocellular diversion, enteroglucagon plasma concentrations are raised. To study further the role of enteroglucagon in promoting small bowel adaptation, enteroglucagon release was stimulated by continuous colonic perfusion of glucose in orally-fed rats. Possible changes in cell proliferation and mucosal mass of an otherwise intact small intestine were assessed by measuring: crypt cell production (CCPR), mucosal wet weight, DNA and protein per cm in jejunal and ileal segments. Enteroglucagon plasma concentration was measured by RIA. Rats were killed eight days after continuous colonic perfusion of 10% glucose (1·8 ml/h) and resultant changes in the intestine compared with those found in 10% mannitol- or isotonic saline – perfused control rats.

Colonic perfusion of glucose provoked a two- to six-fold increase in plasma enteroglucagon compared with control values, without significant change in pancreatic glucagon. In the jejunum, CCPR per hour increased from 21·18±SE 0·6 in controls to 31·87±1·93 after glucose perfusion (p<0·001) and in the ileum from 17·7±1·86 to 30·41±1·79 (p<0·001). Stimulation of crypt cell proliferation resulted in a significant increase in mucosal wet weight from 47·1±SEM 2·5 mg/cm to 63·1±2·1 (p<0·001) in jejunum and from 33·2±1·6 to 44·3±3·0 (p<0·001) in ileum, with corresponding changes in DNA and protein.

We conclude that colonic perfusion of glucose stimulates the release of enteroglucagon and is associated with jejunal and ileal mucosal growth in orally-fed rats. These results suggest that enteroglucagon plays an important role in regulating small intestinal cell proliferation and mucosal mass.

F51
Effect of the intestinal peptide PHI on net intestinal fluid transport in the rat

M GHIGLIONE, N D CHRISTOFIDES, L O UTTENTHAL, K TATEMOTO, AND S R BLOOM (Royal Postgraduate Medical School, London, Karolinska Institute, Stockholm, Sweden) Many factors are involved in the control of the transpor-
oleate emulsion was measured in five dogs without cannula after control antroduodenal transection and after antrectomy while gastric pressure was controlled at 11, 17 and 23 cm H2O. Under both conditions in exp. 1 emptying rose linearly with pressure, yet NaCl emptied significantly faster than glucose. (Mean emptying rate ± SE ml/min. Intact: NaCl = 1.4±8.2±6; glucose = 5±6±2.0, p < 0.05. Diverted: NaCl = 15±3±4.3; glucose = 3±2±1.4, p < 0.05). Thus a major site of chemo-selective resistance lies proximal to the ligament of Treitz. After antrectomy NaCl and oleate emptied significantly faster than before; however, the difference between saline and nutrients was maintained. (Before NaCl = 8±6±2.1; glucose = 3±2±0.7; oleate=4±1±0.7. After NaCl = +2±3±3.7; glucose = 5±5±7.7; oleate=19±3±1.0; *NaCl v glucose or Oleate p < 0.05. †After v. before p < 0.05). Thus resistance does not reside in the antrum or pylorus and clearly the duodenum is implicated.

F53 Porcine histidine isoleucine (PHI) induces secretion in the pig small intestine

A A Anagnostides, K Manolos, N D Christofides, Y Yiagios, R B Welbourn, S R Bloom, and V S Chadwick (Departments of Medicine and Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London) Porcine histidine isoleucine (PHI) is a newly discovered gut peptide with structural similarities to vasoactive intestinal polypeptide (VIP), an established intestinal secretagogue. We therefore investigated the effect of PHI on net water and electrolyte movements. In six anaesthetised pigs, five jejunal, four ileal, and three colonic loops were perfused at 6 ml/min with a bicarbonate/electrolyte solution containing PEG 4000. After a 30 minute equilibration period, net water, sodium, potassium, chloride, and bicarbonate transport were measured in each loop in three test periods; (1) a 30 minute basal period, (2) a 40 minute period during which PHI was infused into the aorta at 30 pmol/kg/min, and (3) a 30 minute post-infusion period. In the basal period there was net absorption of water in the jejunum (−3±4±7±8 μl/cm/10 min) and ileum (−27±8±32 μl/cm/10 min). During infusion of PHI marked water secretion occurred (+6.4±8±54.9 in jejunum and +27±4±34±3 in ileum, p < 0.01), with return to absorption in the post-infusion period (−23±8±23±9 in jejunum and −12±8±13±2 in ileum, ns. v. basal). PHI also caused marked small intestinal secretion of sodium and chloride which again returned towards basal levels in the post-infusion period. Net potassium and bicarbonate fluxes did not change significantly. No consistent pattern of secretion was observed in colonic loops. We conclude that infusion of PHI causes reversible secretion in the porcine small intestine. In view of these finding PHI may play a role in certain cases of secretory diarrhoea.

F54 Prolonged and intermittent stress inhibits human fasting motor complexes (MCs)

R M Valori, M P H Patrick, A Raiman, A Parnham, and D L Wingate (Gastro-Intestinal Research Unit, London Hospital Medical College, London) Previous studies have shown that prolonged mental stress inhibits human fasting upper gastrointestinal motility; however, adaptation occurred after two hours with the single stressor used. Using an ambulant system and three different stressors, we have assessed the effects of prolonged but intermittent stress on the human motor complex. Fasting duodenal and jejunal motility in healthy volunteers (n=8) was monitored continuously for 33 hours using dual pressure sensitive ingestible radiotelemetric capsules. The incidence of fasting motor complexes during seven hours of rest (day 1) was compared with the incidence in a seven hour period (day 2) during which subjects were stressed intermittently by the computer game ‘Asteroids’ (two hours), driving in heavy traffic (two hours), and a delayed auditory feedback technique (one hour). Stress response was quantified using blood pressure, heart rate, and self-reported visual analogue scales. Positive responses, being taken as a 5% increase in blood pressure and 10% in the other variables, were 50% in systolic blood pressure, 60% in diastolic, 70% in heart rate, and 75% in the visual analogue scores. The incidence of motor complexes/hour in day 1 was 0.53±0±09 (mean ± SD) and 0.27±0±18 on day 2, this difference being significant (p < 0.02; Wilcoxon matched pairs signed rank test). The validity of this was further emphasised by the similarity of motor complex incidence during the inter-stress rest periods on day 1. We conclude that the intermittent application of different stressors can significantly reduce the incidence of motor complexes over prolonged periods of time and postulate that these findings may be connected with symptoms of functional bowel disease in susceptible individuals.

F55 Effect of high fat meals on the disruption of fasting motility patterns in man

D F Evans, G E Foster, and J D Hardcastle (Department of Surgery, University Hospital, Nottingham) Feeding disrupts the migrating motor complex in several species including man. It has also been shown in dogs that the percentage of fat in a meal delays the return of the first of these complexes. We have studied the effect of different percentages of fat in meals on the disruption of fasting motility in man. Twenty fasted healthy volunteers were given one of four 600 kcal test meals containing 0, 15, 30, or 60 g of total fat. Antral and jejunal motility was monitored using linked radiotelemetry capsules as previously described. All four meals disrupted fasting activity. The median return to fasting activity indicated by the occurrence of a phase III activity front was significantly shorter for the 0 g and 15 g fat meals compared with the 60 g high fat meal (0g:360 min, range 184–400, 15g:390 min, range 132–576, 60g:424 min, range 344–454) (p<0.04 in all cases). Fifty per cent of the activity fronts were not preceded by antral activity, however, and may not migrate the full length of the small intestine. In this study we have found that only meals with an unusually high fat content cause any significant delay in the return to fasting activity and this may therefore have little clinical significance.

F56 Effect of colonic motor activity on the internal anal sphincter

G G P Browning and A G Parks (Surgical Research Department St Mark's Hospital, London) The myenteric plexus is thought to mediate intestinal peristalsis and the recto-anal inhibitory reflex. The aim of this study was to determine whether peristalsis in the distal colon had any effect on the internal anal sphincter. Fifteen patients were studied. Group 1
consisted of 10 patients with a normal internal anal sphincter and deficiency of the external anal sphincter; seven with pelvic floor neuropathy, and three with cauda equina lesions. Group 2 consisted of five patients with completely normal anal sphincters (normal controls). Intraluminal pressures in the distal colon, rectum, and proximal anal canal were recorded in response to a standardised motility stimulation test. A solution of the surface active agent bicacodyl, applied to the colonic mucosa at 27 cm from the anal verge, was used to stimulate propulsive colonic motor activity.

After stimulation all patients exhibited increased motor activity of a propulsive type. Reflex inhibition of the internal anal sphincter was recorded in response to propulsive sigmoid motor activity in all 10 patients in group 1. The internal anal sphincter inhibition was not abolished by maintaining the lower rectum at atmospheric pressure to prevent distension. In contrast, in group 2, only one patient showed reflex inhibition of the internal anal sphincter; the remaining four patients were observed to voluntarily contract the external anal sphincter resulting in increases in intra-anal pressure.

These results show that a mechanism exists whereby propulsive motor activity in the distal colon reflexly inhibits internal anal sphincter resting tone. Such a reflex may be mediated by the myenteric nerve plexus.

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**ENDOSCOPY**

F57–F63

F57

**Duodenoscopic treatment of acute cholangitis**

A G VALLON, P J SHORVON, AND P B COTTON (Department of Gastroenterology, The Middlesex Hospital, London)

Duodenoscopic sphincterotomy is now routine treatment for duct stones, but its value in patients with acute cholangitis is not widely appreciated.

Of 186 patients referred for endoscopic management during 1979 and 1980, 14 (7.5%) were acutely ill, with pain, jaundice, fever, and leucocytosis. All patients in whom specimens were taken had positive cultures (blood 7/7, bile 13/13). Ages ranged from 47 to 92 years (mean 72 years); nine had previously undergone cholecystectomy.

Nine patients had impacted stones, all with pus; five patients had mobile stones. Sphincterotomy with immediate stone extraction or pernasal biliary drainage was performed without complication, leading to rapid clinical improvement. Stones greater than 15 mm diameter could not be extracted endoscopically in two patients. One was treated surgically; the second was judged to be totally unfit for surgical or other treatment, and died with recurrent sepsis.

Duodenoscopy allows effective management of acute purulent cholangitis, and has potential advantages over percutaneous drainage or urgent surgery.

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**F58**

**Bacteraemia after flexible fibreoptic sigmoidoscopy**

P A FARRAMDS, M J STOWE, M S OSMAN, AND J D HARDCASTLE (Departments of Surgery and Microbiology, University Hospital, Nottingham) Bacteraemia may follow colonoscopy in up to 20% of examinations.

With the increasing use of the 60 cm flexible fibreoptic sigmoidoscope in outpatient departments we felt it important to determine the incidence of bacteraemia in patients undergoing this examination.

One hundred consecutive patients undergoing flexible fibreoptic sigmoidoscopy were given a single phosphate enema half an hour before examination. Ten millilitres of blood were taken from the antecubital fossa immediately before and after the endoscopy and incubated for aerobic and anaerobic organisms. Culture bottles were inspected daily for seven days. Fifty-two patients were male, with a mean age of 60-2 years, range 16-80 years. In only 13 could the sigmoidoscope not be advanced to its full 60 cm. The average time taken for the examination was 8-3 (±3-7 SD) minutes. Fifty-eight patients had significant abnormalities on examination, 16 of which were bleeding at the time. Biopsies were performed in 42 patients. Only one of the blood cultures was positive. This was taken after endoscopy from a woman with florid ulcerative colitis and grew Escherichia coli.

Bacteraemia after flexible fibreoptic sigmoidoscopy is rare and routine prophylaxis for the majority of patients undergoing this examination is unnecessary. Patients with inflammatory bowel disease and a concomitant cardiac abnormality or compromised immune system appear to be at risk, however, and should be given antibiotic prophylaxis.

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**F59**

**Radiological control of oesophageal sclerotherapy: an improved technique**

J D R ROSE, P M SMITH, AND M D CRANE (Department of Gastroenterology, Llandough Hospital, Penarth, S Glamorgan) Intravascular rather than paravasal sclerosant injection is more effective in obliterating varices but some injections will be paravasal, because it is difficult to be certain of the site of injection. This may lead to ulcer and stricture formation. We have, therefore, determined the site of intended intravascular injections radiologically with a 1:3 mixture of 76% Urografin and 3% sodium tetradecyl sulphate in 20 patients. Of 68 injections, 51 (75%) were intravenuous.

Injection into large varices was intravenous in 35 times in 43 (81%) but into small varices only 16 times in 25 (64%).

Fewer complications and faster variceal obliteration might be expected if all injections were intravascular. Eight patients have been treated purely under radiological control. Two millilitres of the sclerosant–contrast mixture were given, but the injection was stopped if a paravasal site were demonstrated. There has been only one ulcer and no stricture formation compared with an incidence of 27% for both complications in our previously reported series. Variceal obliteration was achieved in a mean of 2-8 sessions (range two to four) compared with a mean of six (three to 13) in our earlier series (p<0.002).

Injection under fluoroscopic control demonstrates that a quarter of intended intravascular injections are extravascular, but, if injections are kept within the lumen, complications are reduced and obliteration is achieved in significantly fewer sessions.

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**F60**

**Controlled trial of Nd YAG laser photoocoagulation in bleeding peptic ulcers**

C P SWAIN, S G BOWN, P R SALMON, J S KIRKHAM, AND T C NORTHFIELD (Department of Gastroenterology, University College Hospital, and Norman Tanner Gastroenterology Unit, St James's Hospital, London) The efficacy of Nd YAG laser photoocoagulation in the endoscopic control of haemorrhage from peptic ulcers was
tested in a controlled trial at two centres in London. One hundred and eighty-seven unselected patients admitted consecutively with upper gastrointestinal haemorrhage were submitted to emergency endoscopy. Peptic ulcers were seen in 83. All 47 with stigma of recent haemorrhage (SRH) accessible to laser therapy were included in the trial (11 inaccessible, 25 had no SRH). Prospective stratification was in three groups – those with a visible vessel, those with other SRH, and those in which the clot could not be washed off before therapy. Within each group, ulcers were randomised to conventional management with or without endoscopic laser therapy. Treatment was carried out using 0-5 second laser pulses at 80 watts. Laser and control groups were well matched for other factors known to influence prognosis. Overall, three of 26 treated patients and 10 of 21 control patients rebled (p<0.02). Considering ulcers with a visible vessel, three of 17 treated and nine of 13 controls rebled (p<0.02). Considering other SRH, none of the seven treated rebled compared with one of seven controls. No treated patients but three control patients died after an episode of rebleeding. These preliminary results of this continuing trial suggest that Nd YAG laser has significantly reduced the rebleeding rate in patients with a bleeding peptic ulcer accessible to laser therapy.

F61
Bipolar endoscopic electrocoagulation

D L Morris, P C Hawker, M R B Keighley, AND P W Dykes (The General Hospital, Birmingham) Patients with a non-bleeding 'visible vessel' in the base of a peptic ulcer have a 56% risk of rebleeding and those with active bleeding have an even worse prognosis. In the canine stomach full thickness necrosis was not produced in any of 20 single ACM bipolar probe applications; 10 separate applications to the same site produced serosal injury in only 2/13. Bleeding from canine gastric ulcers (Protell) was controlled in 13/13 cases. Arterial bleeding from canine mesenteric vessels was stopped in 16/17 cases at a rate of <10 ml/min, but in only four of 11 where bleeding was >10 ml/min.

We repeated our study of the histological depth of necrosis in man during elective gastric resection and confirmed the safety of this device.

Endoscopic electrocoagulation has been used in 20 patients without any related complication or death. Nineteen of these presented with a major upper gastrointestinal bleed. Active bleeding was stopped in three out of four cases. Of the 10 patients with a visible vessel at the base of a peptic ulcer who have been coagulated, two have rebled, both at two weeks, but neither required operation. In contrast with the unipolar probe, sticking has not been a problem.

The ACM bipolar probe is safe and is capable of controlling bleeding from peptic ulcers. The ability of this probe to reduce the risk of rebleeding in patients with a visible vessel deserves further study.

F62
Use of needle diathermy wire at ERCP

Andrew Clark (Brighton General Hospital, Brighton, Sussex) Successful cannulation with papillotomy where necessary is not achieved in all patients.

The rate of success varies according to the method of reporting. In this series 60% were cannulated in the system of major interest. Of the remainder, three-quarters (31) were pre-cut with a 'needle' type of diathermy wire, leading to better biopsy of three tumours, images of the system of major interest in three cases, images of papillotomy in 17 cases, and second-go images with papillotomy in seven cases.

This contrasts with the small number of patients who can be helped by conventional pre-cutting with the Classen loop. Complications included one haemorrhage and one case of continuing pancreatitis, but no perforations occurred.

F63
Duodenoscopic palliation of malignant obstructive jaundice with 10 French prostheses

P B Cotton, L Safrany, B Schott, AND J Leung (Departments of Gastroenterology, The Middlesex Hospital, London, and Reinhard Nieter Hospital, Wilhelmsaven, West Germany) Since June 1981, we have attempted to place endoscopic biliary prostheses in 88 high-risk patients with malignant obstructive jaundice. We used an experimental Olympus duodenoscope with a 3-7 mm channel, and 10 French gauge prostheses with double pigtails. Prostheses were inserted in 73 patients (83%), with obstruction of the lower duct (26), midduct (17), and hilum (30).

Jaundice was relieved in 69 patients, but eventually returned in 15 because of tube migration (three), or obstruction (12). Four patients died within 30 days from sepsis (three), and perforation (one). Mean survival was 104 days, and three patients survived more than six months. None has required surgery for duodenal obstruction. Techniques are still being improved.

GENERAL III
F64–F69

F64
Medical therapy of hydatid disease

D L Morris, F Burrows, S Gould, & B Dickson, J Bogan, AND P W Dykes (The General Hospital, Birmingham) While surgery is usually successful in removing solitary hydatid cysts, it is not without hazard. Recurrent or disseminated hydatid disease is a much more serious problem. Mebendazole has shown some effect on Echinococcus granulosus, but a dosage of up to 200 mg/kg/day has been required, and improvement is seldom evident before three months. We have measured mebendazole levels in serum and cyst fluid at operation by radioimmunoassay in six patients taking 50 mg/kg/day. Serum levels were usually below 30 ng/ml and cyst levels below 1 ng/ml.

Albendazole is a new benzimidazole compound. We have used this drug at a dose of only 10 mg/kg/ml for four weeks in four patients. The first patient had multiple cysts in the lung, mediastinum, chest wall, and retroperitoneum demonstrated by CT scan. As well as marked clinical improvement, repeat CT scan at one month showed marked cyst shrinkage. Two of the remaining three have had similar cyst shrinkage. The peak serum levels after one 400 mg dose have usually exceeded 500 ng/ml (high performance liquid chromatography). A progressive fall in CFT titre was seen in three of these cases.

Little mebendazole penetrates into hydatid cysts. Blood levels of albendazole are much higher and our early clinical results are encouraging. This new drug may be an important advance in the management of hydatid disease.
Role of tumours (Hammersmith Hospital, London) Hodgson, D P N demonstrate that abscesses F65 for abscess This improved labelling tropolonate scanning leucocyte scanning. In visible within tomography. The British Society of Gastroenterology accuracy Hodgson, L Lavender, and V S Chadwick (Departments of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London) Indium leucocyte scanning is a recently introduced technique for the detection of intra-abdominal abscesses with a diagnostic accuracy comparable with ultrasound and computer tomography. With currently used cell-labelling techniques (111In acetonate or oxime in saline), however, there is a variable and significant delay in localisation of labelled cells at sites of inflammation and variable sequestration of cells in the lungs. A new method of cell-labelling in plasma using 111In tropolonate has been developed which abolished initial pulmonary sequestration. This improved labelling technique has been used in 60 patients with suspected intra-abdominal abscess to study the rapidity of abscess localisation and the diagnostic accuracy of the technique. Fourteen out of the 60 patients were shown to have abscesses, at laparotomy, at necropsy, and clinically by the spontaneous discharge of pus. 111In tropolonate leucocyte scanning correctly identified 13 (93%) of abscesses. In seven patients abnormal activity corresponding to the site of the abscess was visible within one hour of return of the cells. In 12 other patients extra-abdominal (five) or intra-abdominal (seven) sites of sepsis (other than intra-abdominal abscesses) were demonstrated which accounted for the clinical symptoms. Ultrasound abdominal examination was available in eight patients with proven abscesses and detected five (62.5%), including the single abscess missed on 111In Indium leucocyte scanning. These results demonstrate that 111In autologous tropolonate scanning is a rapid and accurate method of detecting intra-abdominal abscesses.

F65

Indium plasma labelled autologous leucocyte scanning in the detection of intra-abdominal abscesses

S H Saverymuttu, A M Peters, M E Crofton, H J F Hodgson, J P Lavender, and V S Chadwick (Departments of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London) 111Indium leucocyte scanning is a recently introduced technique for the detection of intra-abdominal abscesses with a diagnostic accuracy comparable with ultrasound and computer tomography. With currently used cell-labelling techniques (111In acetonate or oxime in saline), however, there is a variable and significant delay in localisation of labelled cells at sites of inflammation and variable sequestration of cells in the lungs. A new method of cell-labelling in plasma using 111In tropolonate has been developed which abolished initial pulmonary sequestration. This improved labelling technique has been used in 60 patients with suspected intra-abdominal abscess to study the rapidity of abscess localisation and the diagnostic accuracy of the technique. Fourteen out of the 60 patients were shown to have abscesses, at laparotomy, at necropsy, and clinically by the spontaneous discharge of pus. 111In tropolonate leucocyte scanning correctly identified 13 (93%) of abscesses. In seven patients abnormal activity corresponding to the site of the abscess was visible within one hour of return of the cells. In 12 other patients extra-abdominal (five) or intra-abdominal (seven) sites of sepsis (other than intra-abdominal abscesses) were demonstrated which accounted for the clinical symptoms. Ultrasound abdominal examination was available in eight patients with proven abscesses and detected five (62.5%), including the single abscess missed on 111In Indium leucocyte scanning. These results demonstrate that 111In autologous tropolonate scanning is a rapid and accurate method of detecting intra-abdominal abscesses.

F66

Role of hepatic embolisation in advanced carcinoid tumours

P N Maton, M Camilleri, C Haslett, H J Hodgson, D J Allison, and V S Chadwick (Departments of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London) Hepatic arterial embolisation therapy for advanced carcinoid tumours has been evaluated in 11 patients. Ten had flushing, seven diarrhoea, three severe abdominal pain, two wheezing, three right heart failure, and three a pellagroid rash. Before embolisation, patients received p-chlorophenylalanine, cyproheptadine, an aprotinin infusion, methyl prednisolone, and pethidine. Tobramycin, fluoxacillin, and metronidazole were given for 10 days afterwards. After ensuring that the portal vein was patent, selective hepatic embolisation was performed under local anaesthesia. Successful embolisation with tumour necrosis was manifest by mild constitutional symptoms, fever 38°C and leucocytosis 10-7x109 WBC/l. Mean aspartate aminotransferase and alkaline phosphatase levels rose to 800 IU/l (n<45) and 300 IU/l (n<130) respectively. Serum bilirubin levels remained normal. Abdominal pain with hepatic friction rub occurred in three patients and pleural effusion in two. One patient died of septicaemia after stopping antibiotics at seven days. Dramatic improvement in symptoms occurred in eight patients with abolition of flushing and abdominal pain and reduction in diarrhoea (mean stool frequency from 10 to 2/day, n=6). Urinary 5HIAA levels fell from 1132±746 (SD) to 315±178 μmol/day. Symptom relief lasted from one to 24 months (mean 10 months). Recurrent symptoms in two patients were treated by a second embolisation with further remission of symptoms for up to six months. Five patients have died one to 40 months after their first embolisation, as a result of systemic metastases or heart failure.

We conclude that hepatic artery embolisation for carcinoid tumours may produce striking improvement in symptoms. Whether long-term survival is improved is not yet clear.

F67

Ultrasound guided percutaneous pancreatography

W R Lees and P B Cotton (The Middlesex Hospital, London) Ultrasound guided percutaneous pancreatography was attempted on 13 patients. Standard methods of real-time ultrasound guidance were used to puncture the duct with a 22 swg needle. Position of the needle tip in the duct was confirmed by aspiration of several millilitres of juice which was then replaced with contrast (Conray 280). At the end of the procedure the duct was decompressed. Satisfactory pancreaticograms were obtained in 10 patients. All three failures were in patients with a normal calibre duct; in two of these puncture of the duct was achieved but injection of contrast resulted in extravasation. All of the successful procedures were in patients with a dilated duct (range 3-7 mm). In six of these only one pass of the needle was required, and in only one patient needed more than three passes. No complications were recorded in any of the 13 patients. The indications for pancreatography were a ventral pancreas with failure to cannulate the dorsal duct – four patients (includes three failures); a failed ERCP in chronic pancreatitis – one; inadequate ERCP in pancreatic cancer – two; combined ultrasonographic and radiographic guidance for biopsy purposes – six.

Percutaneous pancreatography is a feasible, and, in most cases, easy method of producing high quality pancreaticograms in patients with a dilated duct system.

F68

Endoscopic review of patients having previously undergone gastric surgery

P A Farrands, J S Blake, J D Hardcastle, I D Ansell, and R E Cotton (Departments of Surgery and Pathology, University and City Hospitals, Nottingham) After gastric surgery for benign conditions patients appear to be at risk of developing gastric cancer. Epithelial dysplasia is considered to be pre-malignant and Morson has recently suggested a prospective study to evaluate its role in gastric screening. Six hundred and thirty-six patients under 75 years of age, having undergone gastric surgery for benign peptic disease 15-20 years previously, were identified. Seven patients had died of cancer of their gastric remnant seven to 20 years after operation. One hundred and eighty-nine patients still alive and living in the area were traced and invited to attend for interview; 85 (44.9%) accepted and 71 (37.5%) were gastroscopy and multiple biopsies taken. Of these endoscopy two patients had invasive carcinoma of the stomach, 66 had histological evidence of gastritis (56 (78.8%) chronic atrophic gastritis, 10 (14.1%) superficial gastritis). Thirty-eight patients (53.8%) had intestinal metaplasia and 15 regenerative epithelial cell change. Eleven patients (15.4%) had epithelial dysplasia (six mild, two moderate, three severe) (carcinoma in situ). There was no evidence of any gastric remnant.
The British Society of Gastroenterology

Can benign oesophageal strictures be safely and adequately dilated in the outpatient department?

J M SIMMS, C J STODDARD, J A R SMITH, AND A G JOHNSON (University Surgical Units, Royal Hallamshire Hospital, Sheffield, and Royal Liverpool Hospital, Liverpool)

Benign oesophageal stricture dilatation usually requires hospitalisation and may be followed by patient discomfort and iatrogenic oesophageal perforation. The safety and effectiveness of outpatient department dilatation using Maloney's mercury-weighted dilators has been studied.

Two hundred and fourteen dilatations have been performed in 57 patients with dysphagia and benign oesophageal strictures secondary to gastro-oesophageal reflux. Their mean age was 69-3 years (range 25-89 years), 27 being over 70 years. Macroscopic oesophagitis was confirmed endoscopically and malignancy excluded by biopsy. After a six-hour fast, and with only oropharyngeal anaesthesia, dilatations were performed in an outpatient clinic. Patients were allowed home immediately with instructions to have nothing by mouth for two hours and to return if complications developed. Gastro-oesophageal reflux was controlled medically and dilatations repeated when dysphagia recurred. Between one and 24 dilatations were performed in each patient (mean 3-64).

Dysphagia was improved in all patients and the procedure was well tolerated by most. No oesophageal perforations occurred, the only complications being an insignificant haematemesis in one patient. The interval between dilatations increased with time. This outpatient dilatation technique is effective, well tolerated, and may be safer than other methods of oesophageal dilatation.

Evaluation of ambulatory recordings of gastro-oesophageal reflux: a frequency duration index (FDI)

F J BRANICKI, D F EVANS, J A JONES, A L OGILVIE, M ATKINSON, AND J D HARDCASTLE (Department of Surgery, University Hospital, Nottingham)

Scoring tables for acid reflux have been described but are designed with unjustifiable weighting of supine reflux episodes. We have described a radiotelemetric technique to con-
Gastro-oesophageal reflux was recorded in 20 normal subjects and 20 symptomatic patients with oesophagitis graded at endoscopy and biopsy. Analysis of our 24 hour pH recordings using this scoring system underestimated the severity of reflux, as seven out of 20 symptomatic patients with known oesophagitis were classified as normal.

We have therefore devised the Frequency-Duration Index (FDI). A reflux episode is defined as a fall of at least 2 pH units to less than pH 5. The FDI was obtained by multiplying the frequency and cumulative duration (minutes) of reflux episodes per hour.

In symptomatic patients during the day (0630-2230) the median FDI was 36-21 (range 0-38-158-11) compared with 0-65 (range 0-42-21) in normal subjects (p<0-001). At night (2230-0630) the median FDI was 2-01 (range 0-73-53) in symptomatic patients compared with 0-01 (range 0-0-38) in normal subjects (p<0-001). The index misclassified only one normal subject and two patients (one of whom was thought to have taken antacids) and is considered to be a satisfactory discriminant of abnormal gastro-oesophageal reflux.

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Pharyngo-oesophageal submucosal fibrosis: a possible cause of webs and strictures

DAW EDWARDS (Surgical Unit, Faculty of Clinical Sciences, University College London, London) Fifty-six patients (17 male) with dysphagia had one (15) or two (41) concentric ring constrictions at the pharyngo-oesophageal junction, commonly called 'sideropenic webs'. All had a sensation of obstruction synchronous with the pharyngeal phase of swallowing. Many could sip but not drink. The obstruction was not caused by cicatrization of myopathy. The upper ring was in the plane of the pharyngo-oesophageal junction and the lower 8 to 12 mm (8-12 mm) beyond. The 'webs' appear to be rings of increased resistance to stretch rather than an ingrowth of epithelium and are so similar in position from patient to patient that they are likely to represent an anatomical feature. They may not be visible unless the adjacent more compliant wall is well distended by fluid. Shallow notches are sometimes seen in normal subjects. 'Webs' are often missed at endoscopy and necropsy. Twenty-six also had a cylindrical or posteriorly eccentric narrowing between the webs. Biopsies and one necropsy reveal submucosal fibrosis. One male developed stenosis overnight from haemorrhage from the venous plexus. Evidence of past anaemia was occasional. The concept of 'webs' as epithelial sheets needs revision and the role and origin of submucosal fibrosis should be explored.

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COELIAC

F76 Splenic function and intestinal enzyme activity in coeliac relatives: is there a 'coeliac trait'?

J G O'GRADY, E M CRYAN, F M STEVENS, MCNICHOLL, P FOTTELL, T A O'GORMAN, AND C F MCCARTHY (Medical Research Council, Ireland, Coeliac Unit, Regional Hospital, Galway and University College, Galway) Splenic function was assessed by counting the percentage of 'pitted' erythrocytes in venous blood in 29 healthy...
controls, 29 first-degree coeliac relatives with normal small bowel histology, and 37 coeliacs (both treated and untreated). All coeliacs and relatives were under the age of 25 years and controls under the age of 30 years. The 'pitted' erythrocyte counts were significantly higher in both the coeliacs (7.4±3.6, p=0.0001) and the relatives (6.1±2.7, p=0.0001) than in the control population (3.15±1.7). No significant difference was found between the counts in the coeliacs and relatives (p=0.1).

Small intestinal brush border activity of lactase, sucrase, and alkaline phosphatase was measured in 36 coeliac relatives with normal histology. The levels of activity were compared with normal ranges for age, sex, and site of biopsy and expressed in relation to the mean and 5% confidence level for the appropriate control group. Enzyme activity tended to be in the lower range for all three enzymes and in the case of lactase activity 17% of cases were below the 5% confidence level.

No difference was found between HLA B8 positive and HLA B8 negative subjects for either 'pitted' erythrocyte counts or enzyme activity.

The finding of these abnormalities in healthy first-degree coeliac relatives with normal small bowel histology raises the possibility of the existence of a 'coeliac trait'.

F77
HLA antigens in coeliac disease associated with malignancy

CHRISTINE M SWINSON, P J HALL, PENELAPE A BEDFORD, AND C C BOOTH (Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex) HLA A, B, C, and DR antigen typing was carried out on 45 unrelated patients included in a national register of coeliac patients with malignancy, 20 (44%) of whom had lymphomas and 25 (56%) carcinomas. The results were compared with a group of 48 coeliac patients without malignancy to see whether there are genetic factors separate from those predisposing to coeliac disease associated with the development of malignancy in coeliac patients. The study has also provided data on HLA DR associations with coeliac disease in Britain. No significant differences in HLA antigen frequencies were found between the two coeliac groups, but compared with normal controls, coeliac disease was associated with DR 3 (χ² with Yates correction = 10.5, p<0.001, relative risk 2.45). Thus this study has shown for the first time that, in Britain, coeliac disease is associated with DR 3 and DR 7, and that coeliac patients who develop malignancy share a common genetic background with those who do not, suggesting that the increased susceptibility of coeliac patients to malignancy is determined mainly by environmental factors.

The authors are greatly indebted to numerous clinicians throughout Britain who have sent blood samples from patients under their care, Professor J J van Roon who supplied some of the sera, and to D R A S Peña, for their generous help and cooperation.

F78
Malnutrition caused by occult malabsorption in elderly patients

A MCEVOY AND O F W JAMES (Department of Medicine (Geriatrics), Freeman Hospital, Newcastle upon Tyne) We studied 55 patients who were over 65 years old, admitted to hospital, and found to have malnutrition on the following criteria. Clinical, anthropometric, haematological (Hb, blood film, folates, B12), and albumin + bone chemistry. The commonest problems leading to admission were: 'off feet', 15 patients; diarrhoea (often spurious), 15; weight loss, 13; dementia, seven; bone pain, six. Careful dietary assessment suggested that in 31/55 the cause of malnutrition was dietary deficiency alone. Among the remaining 24 patients, with no previously documented cause for malabsorption, the following tests were carried out: xylose tolerance test (one hour serum sample), 14C-triolein breath test, barium meal and radiology of the upper gastrointestinal tract, endoscopy with small bowel biopsy, and duodenal aspiration for aerobic and anaerobic bacteriology + volatile fatty acids (VFAs), culture was said to be positive if >10³ organisms detected; also 14C-glychocolic acid breath test. If pancreatic disease was suspected ERCP was carried out. The following were the causes for malabsorption: bacterial contamination of small bowel, 17 patients (nine diverticula, four post-gastric surgery, four 'no lump'). Only one had anaerobic organisms with +ve VFAs. Coeliac disease, two; chronic pancreatitis, two; short bowel, one; refused tests, two. Following nutritional support and specific treatment 20/24 malabsorption patients returned home, only 15/31 poor diet patients were able to do so.

We conclude that, in old patients with occult malabsorption, small bowel bacterial contamination is common and treatable.

F79
Gastrointestinal symptoms and specific food intolerance

D A FARAH, I T CALDER, L BENSON, AND J F MACKENZIE (Gastroenterology Unit and Dietetic Department, Royal Infirmary, Glasgow) Forty-eight patients presenting with long-standing gastrointestinal symptoms of unknown cause, principally vomiting and/or diarrhoea, have been investigated for specific food intolerance. Organic disease was excluded as far as possible using routine tests. Patients took a low allergenic diet for up to 14 days. Those patients whose symptoms remitted completely, during this time, were considered likely to have specific food intolerance. Offending specific foods were identified in subsequent weeks by single, weekly, food reintroduction. In seven subjects foods were identified in this way as a cause of symptoms. These were considered suitable for further investigation by randomised, double-blind, specific food/placebo challenge. The challenge was given in the form of opaque capsules as freeze-dried specific food or placebo (glucose). Three capsules were given three times per day for one week or until symptoms became intolerable. In two subjects double-blind challenge confirmed the suspected food as a cause of the patients' typical symptoms. In the remaining five subjects there were substantial placebo reactions. It is concluded that specific food intolerance is a clinical entity, that double-blind challenge with specific foods is feasible, but that the clinical yield in the gastrointestinal clinic is likely to be low.

F80
Effect of dietary fibre on zinc absorption

D A FARAH, M J HALL, P R MILLS, AND R I RUSSELL (Gastroenterology Unit, Royal Infirmary, Glasgow) Dietary fibre, now commonly used in the long-term management of diverticular disease and IBS, may contribute to zinc deficiency by reducing its absorption. Most of the evidence implicating fibre in the aetiology of zinc deficiency is, however, indirect and perhaps inconclusive. The effect of dietary fibre on zinc absorption was therefore studied in normal volunteers using a zinc
tolerance test and whole body monitor to measure the seven-day retention of $^{65}$Zinc ($^{65}$Zn).

Twenty-three subjects (age 21–26 years) were randomised into three groups. All subjects were given 5 μCi of $^{65}$Zn orally in a 10 ml solution of zinc sulphate containing 15 mg of elemental zinc. In addition, group A were given 20 g of wheat bran; group B 20 g of Rice Krispies (a low-fibre food which contains one-tenth the amount of fibre in an equivalent weight of wheat bran), and group C had zinc alone. The seven-day percentage retention (mean ± 1 SD) for the three groups were as follows: group A, 2.43±1.28; group B, 21.45±6.6; group C, 57.9±13.3. All differences were significant (A vs B, p<0.05; B vs C and A vs C, p<0.01). The zinc tolerance test response in group A was flat; in groups B and C there was a significant rise in serum zinc at 90–120 minutes. The areas under the zinc tolerance test curves (mean ± 1 SD in μmol/ml) in the three groups were as follows: group A, 3349±2718; group B, 4004±3571; group C, 5189±3674. All differences were again significant (A vs B, p<0.05; B vs C and A vs C, p<0.01).

We conclude that dietary fibre leads to a significant reduction in zinc absorption which could eventually induce a state of zinc deficiency.

F81

Differential absorption of D-xylose and 3-O-methyl-D-glucose in coeliac disease and acute gastroenteritis

C NOONE, R C BEACH, J BULL, AND I S MENZIES (St Thomas's Hospital Medical School) The rate of gastric emptying and space of distribution after absorption are variables that complicate interpretation of the D-xylose (D-xyl) test. Inclusion of a second marker with susceptibility to these factors should provide correction, but response to the absorptive lesion must differ from that of D-xyl to render a useful discrimination. 3-O-methyl-D-glucose (3mGlc) has been given orally, with D-xyl, for this purpose to fasting subjects as a differential absorption test (2.5+5.0 g, respectively, in 250 ml water: half-dose for infants). Samples of plasma taken at 30, 60, 90, and 120 minutes for adults and of whole blood at 60 minutes for infants were preserved for sugar analysis by thin-layer chromatography.

Plasma D-xyl concentration at 60 minutes gave separation between healthy adults and patients with untreated coeliac disease (0.847±0.119 and 0.277±0.168 mmol/l, respectively, mean ± SD: n=16 for each group) but the D-xyl/3mGlc ratios gave a better within-group reproducibility and between-group discrimination (0.866±0.104 and 0.359±0.129, respectively). Resolution derived from both was greatest at 60 minutes and became progressively less at 30, 90, and 120 minutes. Twenty-five infants (age 3 weeks to 2 years) with acute rotavirus gastroenteritis gave abnormal D-xyl/3mGlc ratios (0.386±0.123) rising to normal (0.760±0.077) after recovery two to four weeks later.

Employment of a D-xyl/3mGlc ratio exploits the relative insensitivity of 3mGlc compared with that of D-xyl to the effects of small intestinal pathology and gives a more reliable index of absorption than that provided by the use of D-xyl alone.

PAEDIATRIC GASTROENTEROLOGY GROUP

Fundoplication in children: before and after assessment using oesophageal pH monitoring

C A CAMPBELL, D OUTRAM, AND V M WRIGHT (introduced by J A Walker-Smith) (Queen Elizabeth Hospital for Children, London) Using a small flexible pH probe, 24 hour monitoring of oesophageal pH was performed in 48 infants and children either in an effort to diagnose suspected gastro-oesophageal reflux or in the assessment of the severity of known reflux. A useful adjunct has been the ability to dynamically monitor the effects of various medical treatments and it has helped to clarify criteria for selection of children for operative correction of gastro-oesophageal reflux.

Results of monitoring in children are presented with special emphasis on six children assessed before fundoplication and 12 assessed after surgery. The results show that oesophageal pH monitoring gives additional useful information regarding gastro-oesophageal reflux and is an easily performed method of assessing the success of treatment including surgery.

Rectal mucosal acetylcholinesterase in Hirschsprung's disease

G DALE, D J SCOTT, AND J WAGGET (Fleming Memorial Hospital for Sick Children, Attic Laboratory, Royal Victoria Infirmary, Institute of Pathology, Newcastle General Hospital, Newcastle upon Tyne) The pre-operative diagnosis of Hirschprung's disease is dependent on the histological evidence of hypertrophied nerve trunks and the absence of ganglion cells. The biopsy may have insufficient submucosal tissue to show that ganglion cells are truly absent; inadequate samples are common.

The demonstration of mucosal nerve fibre proliferation by acetylcholinesterase histochemistry, together with direct assay of acetylcholinesterase activity in mucosal biopsies, have usefully extended the

Fibroptic endoscopy in the early diagnosis of upper gastrointestinal tract haemorrhage in childhood

P J MILLA, J T HARRIES, AND I SPITZ (Institute of Child Health and Hospital for Sick Children, London) Early fibroptic endoscopy is a routine in the management of upper gastrointestinal tract haemorrhage in adult patients. With the availability of more suitable paediatric instruments we have routinely investigated a series of 28 children early in the course of their haemorrhage. We present the endoscopic findings here.

The site of bleeding was localised in 24 cases (86%), which compares well with both adult and paediatric series. This diagnostic score is considerably higher than with other conventional techniques currently employed. Bleeding was not infrequent in infancy, 28% of children presenting were under the age of 1 year, 35% aged 1 to 6 years, and 37% over the age of 6 years. Oesophagitis was the commonest lesion encountered in infants but the bleeding was mild compared with the older children. Over the age of 6 years gastroduodenal ulceration was the commonest lesion and frequently resulted in significant haemorrhage causing both haematemesis and melaena. Aspirin ingestion preceded bleeding in 50% of the children with gastritis, the remainder being sick with severe systemic disease. In this series bleeding in patients with oesophageal varices was variceal rather than due to gastritis or ulcer.

Fibroptic endoscopy gives valuable information regarding the site of the lesion responsible for the bleeding and additionally immediate therapy may be possible. Endoscopy should be performed as a first step investigation in upper gastrointestinal tract haemorrhage.
investigative repertoire. Duplicate rectal suction biopsies were performed on 120 children (newborn to 14 years). One specimen was processed for histochemistry and, in the other, total cholinesterase and acetylcholinesterase activities were assayed using ethopropazine as a selective inhibitor of non-specific cholinesterase.

In patients found not to have Hirschsprung's disease ('normals'), the acetylcholinesterase was independent of age, with a mean value for the group of 6-7 U/l (SD 4-04). In the group with Hirschsprung's disease (16 cases) the mean was 40-3 U/l (SD 28-6, range 8-5 to 130-5). Acetylcholinesterase expressed as a percentage of total cholinesterase activity is a useful additional measurement: normal subjects had a mean value of 50-3% (SD 11-2%, range 40-76%), cases with Hirschsprung's disease gave a mean of 76% (SD 4-7%, range 66-84%).

We conclude that the combination of histochemistry and direct measurement of acetylcholinesterase in rectal biopsies is a useful adjunct to histology, offering the capability of same-day response with fewer samples of inadequate size -- an important consideration in the neonatal period.

Lymphocyte cytotoxicity to autologous hepatocytes in α1 antitrypsin deficiency: a consequence of liver damage

M MONDELLI, A L W F EDDLESTON, R WILLIAMS, G MIELI VERNAGI, AND A P MOWAT
(And Department of Child Health and Liver Unit, King's College Hospital and Medical School, London) The severity of liver disease in children with antitrypsin (α1 AT) deficiency is variable and the mechanism responsible for hepatocyte damage is unknown. To investigate whether cell-mediated immune reactions are involved in the pathogenesis of liver damage, peripheral blood lymphocytes from nine children with liver disease and α1 AT deficiency were incubated in a microcytotoxicity assay with the patients' own hepatocytes obtained from a diagnostic liver biopsy. All had presented with hepatitis in infancy, but were studied from one month to eight years later. Four with histological features of severe neonatal hepatitis were studied within six months of the onset and none had significantly increased lymphocyte cytotoxicity (mean ± SD = 13.2% ± 15.6). Two children, 12 and 15 months old, one with cirrhosis and one with minor histological changes, had values around the upper limit of normal (32% and 34%), while the remaining three children all over a year old, had significantly increased lymphocyte cytotoxicity (55% ± 7%) irrespective of the severity of liver damage (one minor changes and two cirrhosis). Overall there was a significant exponential relationship between percentage cytotoxicity and duration of disease (r=0.81, p<0.01) or age. Thus, cell-mediated immune reactions directed against autologous hepatocytes are present in some children with liver disease associated with α1 AT deficiency but not at the onset. This suggests that such immunological reactions are secondary to the initial liver injury, but whether they may contribute to the perpetuation of hepatocyte damage remains to be established.

Does Indian childhood cirrhosis (ICC) result from viral infection in a copper-laden liver?

M S TANNER, A J E FLOWER, S A BHAVE, AND A N PANDIT
(And Public Health Laboratory and Department of Child Health, Leicester, UK, and Department of Paediatrics, King Edward Memorial Hospital, Pune, India) During a prospective study of paediatric liver disease in Pune, India, 115 pretransfusion sera were examined for evidence of hepatitis A, hepatitis B, Epstein-Barr, and cytomegalovirus infection. Fifty-seven children with Indian childhood cirrhosis had liver copper values of 1836±673 μg/g (controls 8-118 μg/g). Of these, 16 had HAVAB (28%); 19 had EBV IgG (33%), and five EBV IgM; 41 had CMV IgG (72%) and one CMV IgM. None had markers of HBV. Of 35 children with other hepatic disorders in whom liver copper values were 189±298 μg/g, 24 (69%) had HAVAB and 11 HAIgM; 69% EBV IgG, and 57% CMV IgG; five had HBV markers. In controls, 46% had HAVAB, 39% EBV IgG, and 85% CMV IgG.

Wilson's disease in childhood: a plea for early diagnosis

H NAZER, R EDE, A P MOWAT, AND ROGER WILLIAMS
(And Departments of Child Health and Liver Unit, King's College Hospital, London) Although Wilson's disease is a treatable disorder, nine of 15 cases referred with undiagnosed liver disease have died within three to 53 days of admission. To identify features that would enable earlier diagnosis and improvement of management we have retrospectively reviewed these cases. The presenting symptoms were lethargy and malaise, 11 cases; jaundice, 11; abdominal pain, nine; deteriorating school performance, four. The mean duration of symptoms was 4-8 months (range one to 12 months) in fatal cases and 15-4 (one to 18 months) in survivors.

At diagnosis all fatal cases had jaundice and ascites, eight had hepatomegaly, seven splenomegaly, and six oedema. Only one survivor had ascites, two jaundice, two oedema, although four had hepatospleno- megaly. Kayser Fleischer rings were present in six fatal cases and five survivors. All cases had biochemical evidence of liver disease and 14 had low caeruloplasmin and raised urinary copper concentration. Serum bilirubin concentrations, aspartate transaminase, and prolongation of prothrombin time were significantly more abnormal in the fatal cases (p<0.01) as compared with the survivors. Cirrhosis was present in all fatal cases and in four survivors. Penicillamine caused gradual clinical and biochemical improvement in the survivors, except one who required TETA, but in the fatal cases penicillamine and steroids (six cases), BAL (one case), TETA (one case) had no discernible effect.

Wilson's disease must be excluded not only in children presenting with liver disease but also in children with persisting lethargy, abdominal pain, or deteriorating school performance. Specific therapy must be initiated before decompensated cirrhosis develops.

Abnormalities of postprandial small intestinal motor activity in childhood: their role in the pathogenesis of irritable bowel syndrome

T R FENTON, J T HARRIES, AND P J MILLA
(Institute of Child Health, Department of Child Health, and the Hospital for Sick Children, Great Ormond Street, London) Toddler diarrhoea, or the irritable bowel
syndrome in childhood, is the commonest cause of chronic diarrhoea without failure to thrive in childhood, yet little is known of the pathophysiological mechanisms.

Using constantly perfused triple lumen catheters, we have previously shown that the fasting small intestinal motor activity is normal in these children, but, in contrast with controls, their migrating motor complexes are not disrupted by intraduodenal dextrose.

With the same technique we have demonstrated that postprandial activity is induced by constant duodenal perfusion of milk formulae and isosmotic hexose solutions in children with a variety of disorders. When compared with those subjects (n=9) whose migrating motor complexes were disrupted by intraduodenal dextrose (group 1), subjects (n=10) whose migrating motor complexes were not disrupted by intraduodenal dextrose (group 2) demonstrated differences in their postprandial activity.

Normal postprandial activity was induced in only six out of 10 in group 2 vs nine out of nine in group 1. The return of fasting activity (signalled by the appearance of a migrating motor complex) was faster in group 2, occurring in less than 30 minutes in five out of six subjects vs one out of five in group 1. Migrating motor complexes were seen during the duodenal perfusion in four out of 10 of group 2 vs none out of nine in group 1.

We suggest that these abnormalities in postprandial activity play a role in the pathogenesis of the diarrhoea in children with irritable bowel syndrome.

‘M cells’ in rat and childhood follicle-associated epithelium in the small intestine

D JACKSON, J A WALKER-SMITH, AND A D PHILLIPS (Queen Elizabeth Hospital for Children, London) Specialised M cells, found in follicle-associated epithelium are thought to be important in the uptake and presentation of antigen to lymphocytes in the epithelium. They have been shown to exist in adult human Peyer’s patches and, in view of their importance, we have investigated their incidence and cytchemistry in isolated lymphoid follicles in childhood, and compared them with M cells in rat Peyer’s patches.

Isolated lymphoid follicles are frequently found in jejunal biopsies from children and morphologically resemble follicles from Peyer’s patches. They contained, however, only an occasional M cell. In contrast, follicular epithelium from jejunal Peyer’s patches in rats contained numerous M cells, their numbers varying between individual follicles, with up to 30% of the epithelial cells overlying the follicle being M cells. In both children and rats M cell morphology was found to be variable.

An alkaline phosphatase reaction was performed on some of the follicles. It was found that M cells had a reduced amount of alkaline phosphatase activity along their apical membranes compared with neighbouring columnar epithelial cells overlying the follicles.

Thus the incidence of M cells varies greatly in Peyer’s patches from rats and are rarely seen in isolated lymphoid follicles from children. Their incidence may be related to the size and/or functional state of the follicle, as the isolated lymphoid follicles from children tended to be smaller and less often possessed a germinal centre. The reduced alkaline phosphatase activity found along the M cell apical membrane may be a sign of immaturity or of a process of differentiation from columnar cells.

Characteristics of jejunal intraepithelial and Peyer’s patch lymphocytes of neonatal and malnourished rats

M J BRIEUTON AND N LYSCOM (Department of Child Health, Westminster Children’s Hospital, London) The development of antigen handling mechanisms in neonatal gut is essential for the establishment of protective immunity, systemic tolerance to oral antigen, and the avoidance of hyper-sensitivity reactions. As part of an investigation of immunoregulatory mechanisms, T lymphocyte subsets and B cells in the small bowel epithelium and Peyer’s patches have been characterised in isolated cell suspensions from sucking rats and normal and malnourished (6% protein diet) animals. B cell markers and the monoclonal antibodies W3/13, W3/25, and MRC OX 8 were used. The latter are considered to be specific for T cells, T helpers (Th), and T suppressors (Ts) respectively.

Intraepithelial lymphocyte numbers were reduced in the young and in the malnourished. At birth the MRC OX 8 marker was the only one expressed (40%). These unique intraepithelial lymphocytes, which expressed the Ts marker but lacked receptors for the Pan-T marker, were also present among mature IEL (50%). Cells bearing the W3/25 and W3/13 markers appeared from the age of 3 weeks, B cells were rarely seen in intraepithelial lymphocyte preparations. At three weeks Peyer’s patch lymphocytes showed a mature distribution of subsets (18% W3/13, 11% W3/25, 10% MRC OX 8, 49% B). In the malnourished animals the number of intraepithelial lymphocytes expressing MRC OX 8 markers was significantly lower (p<0.01) than in well-nourished controls two and three weeks after weaning. No other differences in lymphocyte subtypes were noted in intraepithelial lymphocytes or Peyer’s patch lymphocytes. The function of intraepithelial lymphocytes is poorly understood but this demonstration of disturbances in their numbers and surface marker characteristics at times when the individual is immunologically compromised suggest the possibility of intraepithelial lymphocyte involvement in mucosal immunity.

Astrovirus within small intestinal mucosa

A D PHILLIPS, S J RICE, AND J A WALKER-SMITH (Queen Elizabeth Hospital for Children, Hackney Road, London) Astrovirus has not been detected within cells of the human gastrointestinal tract, although it is found in stools from children with gastroenteritis, has been associated with diarrhoeal outbreaks, and can produce diarrhoea and seroconversion in adult volunteers.

We now report the findings of astrovirus particles within the small intestinal epithelium of two children admitted for investigation of gastrointestinal problems. One child (JF) had a history of vomiting and weight loss after cow’s milk formula feeding. The other child (RS) had recurrent intermittent diarrhoea. Both developed bouts of diarrhoea in hospital, that of RS following regrading onto cow’s milk. Small intestinal biopsies were performed to investigate the presence of enteropathy. Stools taken for microbiology were found to contain astrovirus on the day of biopsy (JF and RS) and subsequently (RS). Electron microscopy demonstrated astrovirus within epithelium in the lower part of the villus (RS) and exposed surface epithelium of a severe enteropathy (JF). This finding implicates the small intestine as a site of astrovirus replication.

The interpretation of its relevance to the patient is complicated by the presence of other stool pathogens before the astrovirus (E coli 086 (JF) and rotavirus (RS)) and by other confirmed diagnoses (cow’s milk sensitivity enteropathy (JF) and sucrase-isomaltase deficiency (RS)).
These astrovirus infections highlight intercurrent infection as a problem of differential diagnosis and give insight into the interaction between astrovirus and small intestinal mucosa in man.

*In vitro* gluten sensitivity in a patient with familial hypomagnesaemia and unresponsive subtotal villous atrophy (SVA)

P D Howdle, A J Crolllick, M S Losowsky, and J M Littlewood (Departments of Medicine and Paediatrics, St James's University Hospital, Leeds) Familial hypomagnesaemia is believed to be due to a specific defect in intestinal absorption. Jejunal mucosa has been normal in the few cases biopsied. Subtil be villous atrophy in older British children is usually due to coeliac disease. We report a case of familial hypomagnesaemia with subtotal villous atrophy, an association not previously reported.

L W, a 12-year-old daughter of English parents, presented at 2 weeks of age with convulsions. Hypomagnesaemia was diagnosed and magnesium supplements were started. Two infant brothers had previously died of hypomagnesaemia. At 4 years magnesium malabsorption was confirmed; however, malabsorption of fat and xylose and iron-deficient anaemia were also found. Jejunal biopsy showed subtotal villous atrophy, but there was no histo logical improvement 10 and 23 months after starting a gluten-free diet. For the past three years she has taken a normal diet. She has always grown normally with no gastrointestinal symptoms, and has remained on oral magnesium supplements. Jejunal biopsies on three occasions to assess the effect of vitamin and zinc supplementa tion, before re-starting a gluten-free diet have shown subtotal villous atrophy. Each time, mucosa was maintained in organ culture, and was sensitive *in vitro* to Frazer's fraction III, alpha- and unfract ionated gliadin, but not casein, as assessed by changes in enterocyte height, thus behaving similarly to that from untreated coeliac patients.

These results suggest that, despite the lack of response to a gluten-free diet, this child has coeliac disease, and raise the question whether the hypomagnesaemia prevents restoration of the jejunal mucosa *in vivo*.

**Food allergy: the major cause of infantile colitis?**

H R Jenkins, P J Millar, J R Pincott, J F Soothill, and J T Harris (The Hospital for Sick Children, Great Ormond Street, and the Institute of Child Health, London) Ulcerative colitis is rare in childhood and there is an apparent peak incidence in the first year of life, although why this should be is not clear.

In this paper we report eight such patients seen during a three year period, and six of these presented below the age of 4 months; colonoscopy showed the typical appearances of ulcerative colitis.

There was a very close relationship between the introduction of artificial feeding and the onset of symptoms – that is, bloody diarrhoea. Cow's milk protein was the commonest allergen, but soy protein and beef provoked symptoms in three of the cases. Eczema, eosinophilia, and a strong family history of allergy were common. Endoscopic biopsies showed a marked increase of eosinophils in the lamina propria, and IgE antibodies to cow's milk protein were common. The colitis rapidly and completely resolved on an antigen exclusion diet.

These results suggest that food allergy is an important cause of ulcerative colitis in the first year of life, and that an antigen exclusion diet is the treatment of choice. Moreover, the results emphasise the importance of colonoscopy as a diagnostic tool.

**Intestinal permeability in Crohn's disease**

E J Eastham, A D J Pearson, M F Laker, and R Nelson (Department of Child Health, Royal Victoria Infirmary, Newcastle) Intestinal permeability has been investigated in 17 children with Crohn's disease involving the small bowel. The probe molecules mannitol and lactulose were given orally in a moderately hypertonic solution (580 mosmol/l) and urine collected for five hours. Analysis of sugars was performed by gas liquid chromatography. By expressing the result as a ratio of these molecules excreted, patients with active Crohn's disease had a five-fold increase in permeability when compared with a normal control group of 31 children (p<0.001). This was found to be due mainly to an increased lactulose permeability, suggesting changes at junctional complexes and an increase in extrusion zones at the villous tips. Comparing the permeability ratio with a clinical rating of disease severity and separate index of inflammatory activity there was a significant correlation both between patients (p>0.05) and particularly within (p>0.01) patients studied on several occasions. This became more significant when correlating percentage lactulose excretion. We conclude that intestinal permeability, particularly to lactulose, is increased in active Crohn's disease of the small bowel. The test is of clinical value as it is non-invasive, can be performed simply at home, and appears to correlate with disease activity.

**Intracellular particles in childhood inflammatory bowel disease – an enteric micro-organism?**

D C Lewis, J A Walker-Smith, J D Almeida, and A D Phillips (Queen Elizabeth Hospital for Children, London, and Wellcome Research Laboratories, Beckenham) It has often been postulated that a transmissible organism is involved in the pathogenesis of Crohn's disease, however, electronmicroscopy has failed to demonstrate the presence of an infective agent.

Using electronmicroscopy we have found morphological evidence of an enteric micro-organism of a previously undescribed type, in (1) a colonic resection from a child with Crohn's disease, (2) a jejunal biopsy from a child with inflammatory bowel disease, and (3) a jejunal biopsy from a child with a persistent enteropathy of undetermined cause, who has since been lost to follow up.

The putative micro-organism appeared as dense intracellular particles in the apical cytoplasm and microvilli of surface epithelial cells, and as free membrane bound bodies (70–110 nm diameter). Particles also occurred inside protrusions of the microvillous membrane suggesting that they are either budding out of the cell, or are luminal bodies which have fused with the plasma membrane. In our experience no epithelial organelle could account for this appearance. Negative staining electronmicroscopy of an homogenate of a colonic biopsy from case 1 revealed particles of a size consistent with those seen in sections, and when reacted with homologous serum these showed antibody attachment.

The identity of the particle and its relevance to inflammatory bowel disease
Zinc in children with Crohn's disease

N J MEADOWS, C A CAMPBELL, P AGGETT, S CHONG, AND J A WALKER-SMITH (Academic Unit of Child Health, St Bartholomew's Hospital, London) Zinc is an important co-factor in DNA polymerase, RNA polymerase, and thymidine kinase activity, these enzymes being essential for cell replication and protein synthesis. Zinc deficiency may therefore prove to be an important growth-limiting factor in children with Crohn's disease. As there have been conflicting reports of both raised and reduced plasma zinc levels in adults with Crohn's disease, we have studied plasma zinc and copper levels in 21 children with Crohn's disease, monitoring disease activity and growth.

The mean plasma zinc level in the children with Crohn's disease was 10.3 nmol/l compared with the normal mean of 17.5 nmol/l, with 57% of the values less than two standard deviations from the normal mean. The differences are highly significant, but there was no correlation with alkaline phosphatase (a zinc-dependent enzyme), serum albumin, ESR or disease activity index. The plasma copper values in the children were normal. This pattern suggests that true tissue zinc depletion is present, which may be important in the mechanism of growth failure in children with Crohn's disease. Work is in progress to determine the tissue zinc status in the children.

Disaccharidase activities in intestinal fluid reflect local tissue levels

L ARAMAYO, H DE SILVA, G A BROWN, AND A S MCNEISH (Institute of Child Health, University of Birmingham, Birmingham) There are clinical and research circumstances in which it would be desirable to make (serial) measurements of brush border disaccharidase but ethical considerations make repeated jejunal biopsy unjustifiable. We have therefore determined the degree to which disaccharidase activities in jejunal fluid reflect the activities of these enzymes in mucosal biopsies obtained simultaneously from the same site. Duplicate assays of disaccharidase activities were made on fasting, homogenised fluid and conventional mucosal homogenates. Eight children with subtotal villous atrophy (SVA) and 15 children with normal mucosal (N) were studied.

There was a highly significant (p<0.0005) positive correlation (Spearman's rank correlation) between enzyme levels in tissue (T, U/g) and fluid (F, U/l) in all cases (lactase: NT 5.04±1.80 (mean ± SD); NF 4.78±1.52; SVAT 2.54±1.94; sucrase: NT 8.80±2.91; NF 26.41±16.9; SVAT 2.15±1.94; maltase: NT 29.8±10; NF 138±64; SVAT 8.83±5.56; SVAF 66±22.6).

The significant positive correlation between tissue and juice disaccharidase activities suggests that the mucosa is the predominant or sole source of disaccharidase activity in the juice. Preliminary kinetic studies comparing tissue and juice enzyme properties also indicate a mucosal origin for the juice enzyme. We conclude that disaccharidase activities in jejunal fluid reflect local tissue levels and may be a useful alternative procedure when jejunal biopsy is not possible.

Fetal secretory diarrhoea: a new congenital intestinal transport defect

P J MILLA, T R FENTON, AND J T HARRIES (Institute of Child Health and Hospital for Sick Children, London) Secretory diarrhoea may occur from birth. To date the only defect solely of intestinal ion transport which has been clearly defined is of anion exchange in congenital chloride diarrhoea. We present a patient in whom intestinal secretion started in utero.

Transport of water and solutes was studied in the jejunum and rectum of this patient using jejunal perfusion and non-equilibrium rectal dialysis techniques. In the jejunum, water (−35, control +89±10 µl/min/cm) and electrolytes (Na+ −1.26 controls +7.65±1.59; Cl− −1.18 controls +4.62±1.0 µmol/min/cm) were secreted, but glucose and fructose absorption was intact. In the rectum there was impairment of Na+ and Cl− absorption with increased K+ and HCO3− secretion. Further studies of the jejunum using perfusates of high (8-2), neutral (7-1), and low (6-2) pH showed that secretion of hydrogen ion (−0.015 µmol/min/cm) occurred only at high luminal pH with a fall in pH from 8-2 to 7-4; in these circumstances Na+ was secreted (−15.67 µmol/min/cm). At low pH H+ absorption occurred (+0.28 µmol/min/cm, pH 6-2 to 7-1) and Na+ secretion was reduced to −1.83 µmol/min/cm.

These data suggest that Na+/H+ exchange is defective in the proximal jejunum of this patient with only passive movement of H+ ion. We speculate that the secretory diarrhoea is due to a previously undescribed defect of intestinal ion transport.

Functional development of the neonatal gut as measured by electrogenic glucose absorption

A J MAYNE, D A DUCKER, G AUCOTT, C AMIT, W J HUGHES, AND A S MCNEISH (Institute of Child Health, University of Birmingham, and Department of Child Health, University of Leicester) The optimal regime for feeding immature and low birth weight infants is not known. This dilemma would be helped by a better understanding of the absorptive capacities and postnatal development of the immature gut. We have therefore continued our studies of glucose absorption from the small intestine of newborn infants using changes in transmucosal potential difference (PD) as a measure of active glucose transport.

The distal duodenum of infants was perfused via a polyvinyl feeding catheter at 1.5 ml/min with 0.40 mM glucose solutions made isomolar with mannitol and containing 134 mM NaCl. Fullterm (FT) and preterm (PT) infants appropriate for gestational age (AGA) and light for gestational age (LGA) were studied in the first postnatal week. A further group of PTAGA infants was studied for up to six weeks postnatally.

We confirmed our previous results that PDmax was significantly reduced in PTAGA (n=6) and PTLGA (n=9) compared with FTAGA (n=8) infants (p<0.02, p<0.001). In PTAGA infants, PDmax increased from 10.1±1.0 mV during the first postnatal week to 15.2±0.9 in the third postnatal week (p<0.01), followed by a decrease to a new plateau in the fourth (12.0±0.7 mV), fifth (11.5±1.0 mV), and sixth (12.0±0.7) weeks.

We conclude that preterm and growth retarded neonates have a reduced capacity for glucose absorption, compared with fullterm infants. In preterm infants there is a postnatal surge in absorptive capacity for glucose during the second and third postnatal weeks.
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