The British Society of Gastroenterology

The Jubilee Meeting of the British Society of Gastroenterology was held in the University of London on 15–18 September 1987 under the Presidency of Mr John Alexander-Williams. Below are printed the abstracts of the 364 oral and poster communications selected for presentation at the meeting.

INFLAMMATORY BOWEL DISEASE

Enteral nutrition in severe colitis

S S C Rao, C D Holdsworth, and A R W Forrest (Gastrointestinal Unit and Department of Clinical Chemistry, Royal Hallamshire Hospital, Sheffield) Small intestinal absorption and tolerance of enteral nutrition was assessed prospectively in nine patients with severe colitis. After admission, the patients were starved for 24 hours during which stool output was collected. Thereafter 2 l/day of Fortisom standard solution was given enterally via a fine bore tube for six days, after which patients ate a normal diet. During enteral feeding, a 5 g d xylose test and a five day faecal fat estimation were carried out. Stool output, symptom scores, daily weight, Hb, ESR and albumin were also monitored throughout the 10 day study period and prednisolone sulphate was given intravenously. One hour blood xylose and five hour urinary xylose values were normal in all except one patient with Crohn’s disease. Fat absorption was normal in every patient. In spite of enteral feeding, there was a significant reduction in stool weight (p<0.01) and stool frequency (p<0.001) over the 10 day period. There was a significant improvement in symptom scores (p<0.01), ESR (p<0.05) and percentage weight loss (p<0.05). Serum albumin improved [32 (28–37 g/l) v 28 (23–36 g/l), median (range)]. All patients achieved medical remission and one underwent an elective panproctocolectomy. We conclude that even in severe colitis, small intestinal absorption is normal, enteral feeding is well tolerated and parenteral nutrition should not normally be necessary.

Diagnosing inflammatory bowel disease (IBD) with Tc 99m HPMAO labelled leucocytes

M E Roddie, M Peters, M J Carroll, J Calam, H J F Hodgson, and P J Lavender (Depts of Radiology and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, and Amersham International, Bucks) Indium labelled leucocytes are an accurate means of detecting inflammation, particularly inflammatory bowel disease (IBD). Tc 99m as an alternative radioisotope offers advantages of convenience, lower radiation dose, and theoretically higher image resolution. A new Tc 99m chelate, HMPAO (hexamethyl propylene amine oxime) is a moderately efficient leucocyte label with selectivity for neutrophil leucocytes. We evaluated abnormal scans after reinjections of autologous Tc 99m HMPAO leucocytes in 32 subjects with proven or suspected IBD. The normal distribution of radioactivity is similar to that seen with indium labelled cells, with additional activity in urine soon after injection, and some bowel distribution in normal subjects after four hours. Occasional activity in the gall bladder indicates that this normal bowel activity follows biliary excretion of free complex. Bowel activity resulting from labelled neutrophil migration to inflamed areas could be identified much earlier than four hours, however, and as a result IBD could be confidently diagnosed. Twenty five of 32 patients had abnormal scans showing inflamed bowel. The resolution of small bowel involvement is clearly superior to that with indium leucocytes. No false positives or false negatives were encountered.

Use of cloned DNA probes to identify Crohn’s disease microbial isolates

J J McFadden, J Thompson, E Green, S J Hampson, J L Stanford, and J Hermon-Taylor (Department of Surgery, St George’s Hospital Medical School, and of Medical Microbiology, the Middlesex Hospital Medical School, London) Crohn’s disease (CD) microbial isolates in longterm cultures from several laboratories have included bacillary forms of mycobacteria, as well as the scant growth of apparent spheroplasts whose identity has been uncertain. Conventional tests do not readily distinguish between some mycobacteria such as M paratuberculosis and M avium. Restricted total DNA from a CD mycobacterial bacillary isolate was used to generate a genomic library in pGEM-1. Resulting specific cloned DNA probes precisely distinguished different mycobacteria on the basis of restriction fragment length polymorphisms (RFLP). A novel insertion element of about 1.5 kb (pMB22) was identified, repeated 10–20 times throughout the mycobacterial genome. DNA restricted and probed with pMB22 gave a simple banding pattern RFLP identical in the DNA from each of three independent CD, and three Johnes’s disease M para isolates, but not other mycobacterial DNA suggesting a specific relationship between this insertional element and pathogenicity. Similar studies on nanogram quantities of DNA from one CD spheroplast isolate using a novel cloned DNA probe for M para 16S ribosomal RNA identified the spheroplasts as mycobacterial but distinct from any known mycobacteria so far examined. Crohn’s disease derived mycobacterial isolates appear heterogenous.

Adhesion of colitic E. coli (EC) to isolated human colonicocytes

D A Burke and A Traxon (Gastroenterology Unit, The General Infirmary, Leeds) Tissue culture and buccal epithelial cell adhesion assays have shown that E. coli (EC) isolated from patients with ulcerative colitis possess an adhesive property. In this study human colonicocytes have been used to assess in vitro adhesion. Colonicocytes from mucosal biopsies were isolated by gentle agitation in the presence of hyaluronidase at 37°C. The test bacterial suspension was incubated with the isolated colonicocytes in Ham F10 at 37°C for 30 minutes. Adhesion was assessed under phase contrast and expressed as the number of bacteria adherent to brush border (BB) and BB/basolateral (BL) adhesion ratio. The BB score of 12 colitic EC isolates to colitic colon, mean=2.03, is significantly higher than control EC, mean=0.28, p=0.001. The BB/BL ratio of colitic EC.
mean = 0.33 compared with a mean of 0.1 for control EC is significantly higher, \( p = 0.001 \). Buccal epithelial cell adhesion ability correlates with both the BB adhesion index and the BB/BL ratio, \( p = 0.001 \). This study shows that colitic EC have a greater ability to adhere to human colitic colon than controls. The higher BB/BL ratio for colitic EC suggests that adhesion is specifically directed to the brush border. These data support the view that EC may have a role in the pathogenesis of this disease.

Delayed-release 5-aminosalicylic acid (5-ASA) and sulphasalazine (SSZ) in the treatment of mild to moderate ulcerative colitis (UC) relapse

S A RILEY, V MANI, M J GOODMAN, AND L A TURNBERRY (University Department of Medicine, Hope Hospital, Salford; Leigh Infrmary, and Bury General Hospital, Manchester) Sulphasalazine is of benefit in UC relapse but side effects may limit its use. 5-ASA appears less toxic. We have therefore compared SSZ, equivalent dose 5-ASA and high dose 5-ASA in mild to moderate UC relapse.

Sixty one patients (32M:29F, aged 20–78 years) were randomly allocated to either SSZ 2 g, 5-ASA 800 mg or 5-ASA 2 g daily in a double blind four week trial. One patient defaulted leaving 19 SSZ, 20 5-ASA 800 mg and 21 5-ASA 2 g for analysis. Groups were comparable for age, sex, extent of disease and pretrial SSZ intake. Six patients were withdrawn, four SSZ (two deterioration, two side effects) and two 5-ASA 2 g (deterioration).

Within treatment comparisons revealed significant improvement of (a) sigmoidoscopic grade in the SSZ group, (b) rectal bleeding and sigmoidoscopic grade in the 5-ASA 800 mg group and (c) stool frequency, rectal bleeding and mucus and sigmoidoscopic grade in the 5-ASA 2 g group. Symptomatic remission occurred in 21% SSZ, 30% 5-ASA 800 mg and 42% 5-ASA 2 g (p<0.05 v SSZ).

Greater improvement of rectal bleeding occurred in the 5-ASA 2 g than SSZ group (p<0.05). Side effects, however, were similar in the three groups.

High dose 5-ASA is more effective than SSZ in the treatment of UC relapse.

Causes and prevention of postoperative fistulae in Crohn's disease

FRANCOISE HÉYÉN, M C WINSLET, HILARY ANDREWS, R N ALLAN, M R B KEIGHLEY, AND J ALEXANDER-WILLIAMS (The General Hospital, Birmingham) From a series of 59 patients with enterocutaneous fistulae complicating Crohn's disease, 31 occurred in 23 patients within a month of operation.

Four were referred having presented the fistula within 10 days of appendicectomy by surgeons inexperienced in Crohn's disease. All were ileocutaneous, three had resection and one a stricuoplasty; all resolved.

Suture line leakage accounted for 18 fistulae and nine, presumed to be caused by operative trauma, originated from a dissected area of gut not affected by Crohn's disease. Previous reports suggest that the majority of such fistulae will heal spontaneously. In this series, however, only 12 of the 27 resolved without further operation.

The principal predisposing factors in suture line leakage were adjacent septic foci, hypoproteinaemia and colonic anastomosis. In some severely compromised patients a primary stoma with delayed anastomosis might avoid leakage.

In another series of patients having extensive dissections, occult operative trauma has been rendered overt by CO₂ distension of the gut and underwater inspection (cycle tyre puncture manoeuvre). All such detected bowel breaches have been sutured without subsequent fistulae. We suggest that routine adoption of the insufflation manoeuvre might have prevented five of the nine operative trauma fistulae in this series.

Stricuoplasty for Crohn's disease – a nine year experience

T C B DEHN, N J MCN MORTENSEN, M G W KETTLEWELL, D P JEWELL, AND THE LATE E C G LEE (John Radcliffe Hospital, Oxford) The role of stricuoplasty (SP) is controversial in the management of obstructive Crohn's disease (CD). In Oxford, since 1978, 20 patients have undergone 26 SP operations with a median follow up of 30 (range 2–102) months. Crohn's disease had been present for 0–240 (median 12) months. Sixteen patients previously had resections for CD. Eighteen patients received high dose parenteral steroid therapy preoperatively. Strictures were confirmed before surgery by small bowel enema and identified operatively by intestinal intubation. The median number of strictures identified at surgery was two (range 1–17): 16 patients had one SP, 10 patients between two and seven SP. The length of stricture plaited bowel ranged from 1–17 (median 3) cm. Intestinal resections were performed concurrently in 12 patients. Four patients subsequently required a further 14 SP between 12 and 36 (median 18) months after the initial SP. All but one of the previous SPs were patent. No postoperative complications arose from the SP sites. Intrapertitoneal abscesses developed in one patient from a duodenal leak. Our further experience indicates that SP is an effective and safe procedure which has a place in minimal surgery of both active and inactive CD, provided no distal obstructing lesions are overlooked.

LIVER I

Effect of hepatic artery embolisation on survival in carcinoid syndrome

M COUPE, A HEMMINGWAY, H J F HODGSON, AND D J ALLISON (Depts of Medicine and Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, London) Hepatic artery embolisation relieves systemic hormonally mediated symptoms in the carcinoid syndrome, and local symptoms of hepatic pain. We document here the effect of this procedure on survival in a retrospective survey of 63 patients with carcinoid syndrome seen in one centre over 10 years. Twenty four underwent hepatic artery embolisation, and in a further six embolisation was intended, but technically not feasible (portal vein obstruction or inadequate arterial access). The indication for embolisation was severe systemic symptoms poorly controlled by pharmacological therapy, or marked local pain. Overall, in those patients followed to death, the mean survival from symptom onset was longer in those undergoing hepatic artery embolisation, but this was not statistically significant (58.7±9.7 (SEM) months n=18 v 44.5±9.6, n=11). A more accurate comparison can be drawn between those patients successfully embolised, and those in whom the procedure was unsuccessful, comparing survival from the angiographic procedure. There was no difference in survival between these two groups (embolised mean 18.0±3.26 months n=18 v embolisation technically impossible mean 19.6±6.5 months n=6). This study confirms that the hepatic artery embolisation does not prolong survival in the carcinoid syndrome, despite its effectiveness in relieving symptoms.

Cellular chemotaxis to bile after liver transplantation

Gut: first published as 10.1136/gut.28.10.A1328 on 1 October 1987. Downloaded from http://gut.bmj.com/ on April 15, 2022 by guest. Protected by copyright.
D H ADAMS, D BURNETT, R A STOCKLEY, AND E ELIAS (Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham) The mechanisms of cell recruitment to liver allografts during rejection are poorly understood. Chemotactic factors may be important but have not been studied in man. As the cellular infiltrate is centred on bile ducts we have looked for chemotactic activity in serial bile samples from 13 liver transplant recipients.

During nine episodes of graft rejection, bile became chemotactic for both neutrophils and mononuclear cells when compared with bile taken from seven stable transplants (neutrophils rejection: range 2-2-22, median 4.2 x 10^6 control; stable: 0.44-2.7, median 1.73; p<0.005; monocytes rejection: 0.89-7.03, median 2.12; stable: 0.55-2.63, median 1.08; p<0.025).

Bile taken two to four days before clinical rejection was chemotactic for lymphocytes (2.3-8.9, median 3.2; p<0.001) but during clinical rejection inhibited chemotaxis (0.14-1.08, median 0.74, p<0.025) when compared with bile from stable transplants (0.97-1.8, median 1.4).

We conclude that (1) chemotactic factors are important in cell recruitment to rejecting liver grafts. (2) Lymphocytes are attracted to the graft before the onset of clinical rejection. (3) During clinical rejection lymphocyte chemotaxis is inhibited whereas other cells are attracted to the graft.

Management of increased cerebral blood flow in patients with fulminating hepatic failure

R J EDE, C D GOVE, AND R WILLIAMS (Liver Unit, Kings College Hospital and Medical School, London) Raised intracranial pressure (ICP) is a major cause of mortality in patients with fulminating hepatic failure (FHF) and is generally attributed to the development of cerebral oedema which is a frequent autopsy finding. It has been suggested recently that ICP might also be increased as a result of dilatation of the cerebral blood vessels resulting in increased cerebral blood flow (CBF). We therefore determined CBF using the iv 133Xe clearance technique in 15 patients with FHF caused by paracetamol overdose (10), viral hepatitis (three), and halothane hepatitis (two). Patients were studied in grade four encephalopathy after intubation and mechanical ventilation. In every case CBF was increased with a mean value of 20.1 ml/100 g brain/min (range 137-310) over a PaCO₂ range of 4.5-6.0 kPa (CI normal value of <1.1 ml/min). Cerebral blood flow values did not differ significantly between the three main aetiological groups. Cerebral autoregulation in response to changes in PaCO₂ was assessed in seven patients: CBF increased linearly over the PaCO₂ range 2.5-7.5 kPa in all but one patient in whom this autoregulatory response was lost a few hours before death. Raised CBF was reduced by vigorous hyperventilation and more rapidly by iv Althesin (we have shown that both these measures reduce increased ICP in FHF). These data indicate that increased CBF contributes to raised ICP in patients with FHF and have important therapeutic implications for the management of patients with this life-threatening complication.

Distribution of calcitonin gene related peptide (CGRP) and substance P-containing nerves in liver: an immunohistochemical study

A D BURT, M GILLON, E WISE, J M POLAK, AND R N M MACSWEEN (University Department of Pathology, Western Infirmary, Glasgow, Lab for Cell Biology and Histology, Free University of Brussels (VUB), Belgium, Department of Histochemistry, Royal Postgraduate Medical School, London) We have investigated the distribution of nerve fibres containing the regulatory peptides, calcitonin gene related peptide (CGRP) and substance P in guinea pig and rat livers. These peptides are closely associated with afferent neurones in the peripheral nervous system. The livers of Dunkin Hartley guinea pigs and Wistar rats were perfusion fixed with 0.4% paraformaldehyde. Tissue blocks were washed in 15% sucrose and frozen in liquid nitrogen. Polyclonal rabbit anti-CGRP and anti-substance P antibodies were used at dilutions of 1:200 to 1:800 on 5 and 12 μm sections with an indirect immunofluorescence technique. CGRP and substance P containing fibres were identified within portal tracts in the livers of both species. Fibres were most frequently seen around hepatic artery branches but were also seen in close proximity to bile ducts and portal vein branches. No intra-acinar fibres were identified. There was abrogation of staining for both peptides in the livers of rats treated in the neonatal period with the sensory neurotoxin capsaicin. These results indicate that the intrahepatic vasculature but not the liver parenchyma receives a peptidergic sensory nerve supply.

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Portal tract lymphocyte populations in primary sclerosing cholangitis

J A SNOOK, K A FLEMING, A HERLYET, P KELLY, D P JEWELL, AND R W CHAPMAN (Department of Gastroenterology and Nuffield Department of Pathology, John Radcliffe Hospital, Oxford) Recent evidence suggests that immunological mechanisms may be of importance in the pathogenesis of primary sclerosing cholangitis (PSC). We have previously shown that patients with PSC have reduced numbers of CD8⁺ cells in peripheral blood. Here, portal tract lymphocyte subsets have been analysed in cryostat sections of liver biopsies using monoclonal antibodies and an immunoperoxidase technique. Liver biopsy sections from nine patients with precirrhotic PSC, nine patients with primary biliary cirrhosis (PBC) and seven patients with histologically normal livers were examined. The T lymphocyte was the predominant portal tract mononuclear cell in all three groups. Mean total T lymphocyte counts per portal tract (/+ SD) were increased in both PSC (173±105) and PBC (210±110) compared with controls (42±27). Similar increases were seen for both CD4⁺ and CD8⁺ cells so that the CD4⁺: CD8⁺ ratio was 1.49 in PSC, 1.89 in PBC and 1.63 in controls. In contrast, B lymphocyte counts were low in PSC (8+/−14), PBC (9+/−14) and controls (1+/−1). These results suggest that T cell mediated immune mechanisms may play an important role in the pathogenesis of PSC. In contrast with the situation in peripheral blood, the portal tract CD4⁺: CD8⁺ ratio is similar in PBC and PSC.

Changes in the hepatic haemodynamics with the development of liver metastases

D M NOTT, S A JENKINS, S GRIME, J YATES, D W DAY, J N BAXTER, AND T G COOK (University Departments of Surgery, Pathology and Nuclear Medicine, Royal Liverpool Hospital, Liverpool) The ratio of the hepatic artery flow (HAF) to total liver blood flow measured by dynamic scintigraphy, the hepatic perfusion index (HPI), is reported to predict the presence of occult liver metastases in patients with colorectal carcinoma. The aim of this study was to determine the mechanisms responsible for the alteration in the HPI with the development of micrometastases. Metastases were induced in rats by an intraportal injection of 8×10⁶ Walker carcinosarcoma cells. Animals were studied at two, four, and six days post inoculation. The HPI was...
The British injection stases were artery aggregated albumen inoculation. At 0-001). Superoxide release significantly to exposed hyde induced neutrophil pH 7-4, (p<0-01) n=16). Penicillamine binding of this hyde altered (5/1 molar ratio) penicillamine and cysteine, cysteine, isoleucine, valine, alanine, glutamic acid, serine, and glycine. We have studied the effect of penicillamine and cysteine in modifying neutrophil superoxide release in response to acetaldehyde altered rat hepatocyte membranes. Liver membranes were preincubated in 1 mM acetaldehyde±equimolar or excess (5/1 molar ratio) penicillamine or cysteine, pH 7-4, two hours, 18°C; washed and then exposed to neutrophils with superoxide release measured by cytochrome c reduction in the presence or absence of superoxide dismutase.

Pre-exposure of the membranes to equimolar penicillamine and acetaldehyde significantly reduced superoxide release compared to acetaldehyde alone exposed membranes from 154±16 (mean±SEM) to 77±10 mmol O2/106 cells/min n=9, p<0-01. Pre-exposure to equimolar cysteine significantly reduced superoxide release to 94±12, n=9, p<0-01. A further reduction occurred when in molar excess (penicillamine 33±7, cysteine 57±13, n=9). These findings could have potential benefit in limiting neutrophil stimulation in alcoholic hepatitis.

Measurement of pepsin synthesis in man using 1-13C-leucine

M E CORBETT, E J S BOYD, J G PENSTON, K G NORMSLEY, AND M J RENNIE (Departments of Physiology and Therapeutics, Dundee University, Dundee, Scotland) We have studied the effects of increasing doses of pentagastrin (Pg) on gastric secretion of acid, pepsin and total protein. In addition, we have used the rate of incorporation of 1-13C-leucine into the YCA-insoluble fraction of the gastric aspirate as an index of pepsin synthesis.

On separate days 10 subjects received Pg 0, 0-25, 0-5, 1-0, 2-0, or 4-0 μg/kg/h together with a primed infusion of 13C-leucine 0-25 or 0-5 mg/kg followed by 0-25 or 0-5 mg/kg/h respectively. Infusions were continued for 210 min. Gastric juice was aspirated in 30 min batches. 13C enrichment of plasma keto-isocaproate was measured every 30 min. Affinity chromatography confirmed that 13C-leucine was incorporated solely into pepsin.

The dose of Pg required for half maximal acid secretion was 0-13 μg/kg/h, and for half maximal pepsin secretion was 0-10 μg/kg/h. Incorporation of 13C-leucine into the TCA precipitate was linear with time, and the rate was proportional to the plateau 13C enrichment of plasma keto-isocaproate. Pg did not significantly alter from basal the rate of incorporation of 13C-leucine into pepsin. These findings suggest that increased pepsin secretion in response to increasing doses of Pg is not caused by increased pepsin synthesis, but is attributable to recruitment of cells having similar synthetic activity.

Gastric acid regulates postprandial somatostatin release in man

M R LUCEY, P D FAIRCLOUGH, AND J A H WASS (St Bartholomews Hospital, London) The role of gastric acidity in mediating release of somatostatin like immunoreactivity (SLI) in response to orally ingested nutrients in man is uncertain. We studied in healthy men the effect of cimetidine (100 mg/h iv for four hours) on circulating SLI levels basally and with ingestion of a mixed meal. In some studies, intragastric pH was measured radiotelemetrically and either 0-1 N HCl or 0-9% NaCl infused intragastrically. In further studies, an intraduodenal infusion of fat was given with/without iv cimetidine.

Cimetidine (C) reduced meal-stimulated SLI levels: meal alone: 83±10% min. mean integrated increment from basal. ±SE; meal+C: 51±12% min. p<0-05 (n=12). Intragastric infusion of HCl ameliorated the effect of C on mean postprandial gastric pH: meal alone: 2-21; meal+C: 3-79; meal+C+HCl: 3-15; and prevented the cimetidine-induced reduction in postprandial SLI levels. Meal alone: 75±18% min. meal+C: 28±15% min. meal+C+HCl: 65±12% min (n=6). Cimetidine did not affect the rise in SLI levels during intraduodenal fat infusion (n=5). These data suggest that (1) cimetidine reduces postprandial SLI secretion indirectly by altering intragastric acidity, (2) intragastric acid is a factor regulating nutrient stimulated SLI levels in man.
suggest that (1) fat stimulates SLI release from the isolated perfused rat stomach, (2) this action is dependent on presentation of the stimulus to the lumen, (3) stimulation of SLI release by fat does not depend on its metabolism or absorption.

Mechanisms governing the biphasic pattern of gastric emptying after truncal vagotomy and pyloroplasty

N Parr, S Grime, M Critchley, J Baxter, and C Mackie (University Department of Surgery and Department of Nuclear Medicine, Royal Liverpool Hospital, Liverpool) After truncal vagotomy and pyloroplasty (TV+P) gastric emptying (GE) of liquids is biphasic, with rapid early GE often producing post-vagotomy symptoms. Factors restricting this phase and provoking transition to the second, slow phase are unknown. We investigated the contributions of small bowel resistances, osmoreceptor feed back and sympathetic inhibitory reflexes to small bowel distension. Sixty GE studies were done, using gamma camera imaging of radio labelled 15% dextrose on six dogs with TV+P and fitted with proximal duodenal canulae. With the canula closed GE (%) was initially rapid, followed by stasis (15 min 32±5.3, 60 min 34±4.8, mean±SEM). Opening the canula alone, produced precipitous GE (76±4.2 p<0.001, 88±2.6 p<0.001 ANOVA). With distal duodenal instillation of 15% dextrose at a rate equivalent to GE with the canula closed, GE remained faster than in the initial studies (50±7.0 NS, 65±6.8 p<0.01), but was slower than with diversion alone (p<0.05). Normal saline instillation did not delay GE (78±10.6, 90±5.4). Finally, duodenal instillation of 15% dextrose prior to ingestion of the test meal caused slower initial emptying than in canulla closed studies, without subsequent stasis (24±4.5, 47±10.6). These results indicate that after TV+P, small bowel resistances play a significant role in controlling GE. Osmoreceptor responses persist after TV+P, but sympathetic inhibitory responses are not invoked.

Gastrin – in vitro and in vivo studies in gastric and colorectal cancer

S Watson, J. Durrant, D L Morris, and G Geroulakos (Departments of Surgery and Cancer Research, University Hospital, Nottingham) Gastrin is trophic for both gastric and colorectal carcinomas in animal models but in vitro studies have been less reproducible. The recent innovation of synchronisation of cell cultures with thymidine was used to study nine gastric or colorectal cell lines; no stimulation was seen with pentagastrin or G17. Using the synchronised assay, however, two cell lines showed an increase in growth rate (selenomethionine incorporation) to G17 10 μg/l of 110 and 120%. The most responsive of the cell lines was xenotransplanted into mice and half the animals treated with G17 10 μg/day. Not all xenografts grew but of the five fastest growing tumours in each group the diameter of the tumours was significantly greater in the treated group by 17 days (p<0.01). When cells from this xenograft were cultured in vitro a 148% increase in growth was seen. We also studied the in vitro growth of freshly disaggregated human tumour cells and showed a response to pentagastrin in one gastric and ½ colorectal tumours. This response was retained at in vitro passage 2 but lost by passage 6. Gastric and colorectal tumours are often sensitive to gastrin in vivo – this stimulation is often lost or reduced in in vitro cultures.

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N-methyl-N’-nitro-N-nitrosoguanidine (MNNG) induces changes in rat and human pepsinogen phenotypes

J DeFize, J K Derodra, and R H Hunt (McMaster University, 1200 Main Street W, Hamilton, Ontario, Canada) A characteristic human pepsinogen (PG) phenotype has been described in association with gastric cancer and MNNG is known to produce gastric tumours in the rat. We describe changes in rat and human PG phenotypes, induced by MNNG in in vivo rat experiments and in in vitro cultures of both rat and human chief cells. Rats were fed MNNG or placebo for five different time periods. PG phenotypes and histological status of the mucosa were determined from open biopsies taken under anaesthesia before, during and after MNNG. The fastest electrophoretic band decreased or disappeared as early as three weeks after MNNG. The changes, observed in 17 of 32 rats, were permanent and consistently associated with gastric tumour lesions observed 10 months later (17 of 17). Chief cells were cultured in the absence or presence of MNNG, which induced similar PG phenotype changes in both rat and human chief cells after 7–10 days. In human chief cells, a decrease of the Pg band, which is consistent with the ‘carcinogenic’ phenotype, was observed in two of six preparations, treated with MNNG.

We conclude that MNNG induced phenotype changes reflect mutations in the pepsinogen genes. The changes precede gastric tumours and should be investigated as a marker for the early onset of gastric cancer.

Changes in mucus glycoprotein biosynthesis at the tumour site in gastric cancer

N K Dhiri, R I Sidebotham, J Spencer, and the Late J Schrager (Department of Surgery, Royal Postgraduate Medical School Hammersmith Hospital, Du Cane Road, London) Immunohistochemical investigations and studies of cultured tumour cell lines have shown that carbohydrate biosynthesis of mucus glycoproteins is altered in gastric carcinogenesis. To extend these observations we have examined the structures of mucus glycoproteins from non-malignant mucosa (20 specimens; individuals with benign peptic ulcer, or disease free), and from uninvolved mucosa (33 specimens) or tumour site (32 specimens) in patients with stomach cancer. Carbohydrates and amino acids were measured by gas chromatography and autoanalysis. From this, the weight of carbohydrate associated with representative polypeptide core segments of equal length was determined. A mean difference of 29% (p<0.0001) occurred between glycoproteptides from uninvolved mucosa and tumour site. This resulted from a reduction in numbers of (1) carbohydrate chains, from a mean of 343 to 276 chains/1000 amino acid units (p=0.01), associated with a decrease of serine and threonine residues in the polypeptide core and (2) structural units per carbohydrate chain, from a mean of 6.85 to 6 (p=0.01), attended by a decrease of fucosyl groups, from a mean of 1.6 to 1.05 per chain (p=0.02) in glycopolypeptides from the tumour site. Differences between mucous glycopolypectides from non-malignant and uninvolved mucosa were small, and not statistically significant. These data show that carbohydrate biosynthesis is curtailed, and that biosynthesis of the polypeptide core may be abnormal, in mucus glycoproteins produced at the tumour site in gastric cancer.

Lactulose/mannitol: an ideal screening test for coeliac disease?

J D Juby, J Rothwell, and A R Axon (Gastroenterology Unit, The General
Infirmary, Leeds) Changes in intestinal permeability are shown by differential sugar absorption tests in coeliac disease, but are not ideal for screening as the sugars are often difficult to analyse and chromatography is usually required. We describe a chemical technique for analysis of lactulose and compare the lactulose/mannitol (La/Ma) test to a standard cellbiose/mannitol (Ce/Ma) test in two groups: (1) newly presenting coeliacs (17); (2) healthy controls (12). The test solution comprises 5 g lactulose, 2 g mannitol, and 22.3 g glucose in 100 ml water (hyperosmolality enhances discrimination between coeliacs and normals). This is ingested after a six hour fast and urine collected for five hours. Lactulose is measured by an enzymatic method and mannitol by spectrophotometry, the result being expressed as a ratio which eliminates extraneous factors (gastric and bladder emptying, etc). The median La/Ma test was 0.080 (range 0.02–1.356) in coeliacs and 0.016 (range 0.004–0.028) in controls (p<0.001) as compared with a median of 0.112 in coeliacs (range 0.024–0.720) and 0.01 in controls (range 0.008–0.024) for the Ce/Ma test (p<0.001). There is no significant difference between the two tests. This method fulfils the criteria for an ideal screening test, it is of low cost, simple to do and analyse, and is non-invasive. It compares favourably with the Ce/Ma test which is highly sensitive and moderately specific.

Developmental changes in the villous uptake or iron and enterocyte iron binding proteins in the guinea pig duodenum

S K SRIAL, E DERNAM, AND O EPSTEIN (Royal Free Hospital School of Medicine, London) In a previous in vivo study we showed that the rate of iron uptake by neonatal guinea pig duodenum is substantially higher than that of adults. We proposed that the failure of postnatal adaptation in man might be a factor in the pathogenesis of haemochromatosis. This study reports the use of autoradiography to define changes in villous localisation of iron uptake and gel filtration of enterocyte soluble supernatant (SSN) to study the ontogeny of iron binding proteins in the guinea pig duodenum.

Autoradiography revealed that whilst all neonatal enterocytes took up Fe⁺, only those in the top half of adult villi take up the isotope.

Gel filtration of SSN on Sepharose 6B indicates that in the newborn guinea pig the major Fe⁺-binding peak has a low molecular weight (MW≤12,000) accounting for 70–80% of the eluted counts. In contrast, the major Fe⁺-binding peak in adults was a high molecular weight (MW≥450,000 possibly ferritin) accounting for 62% of eluted counts. The differences in iron binding proteins and iron uptake along the villus might account for the difference between neonatal and adult iron absorption described in vivo. Similar studies in haemochromatosis might shed light on its pathogenesis.

Localisation of VIP binding sites in human and guinea pig gut using in vitro autoradiography

R P ROSS, A J BISHOP, M A GHANDEL, S R BLOOM, AND J M POLAK (Departments of Histology and Medicine, RPMS, Hammersmith Hospital, London) Despite numerous studies of peptide receptors by binding techniques on isolated membrane preparations, little information is available on their precise localisation. In this study, we have used the technique of in vitro autoradiography to localise receptors for vasoactive intestinal peptide (VIP), one of the most abundant peptides present in the enteric nervous system, in human and guinea pig small and large intestine, where it is known to have potent actions. Unfixed cryostat sections were incubated with radiolabelled ([125I] ligand at a concentration of 1 nM. Specificity of binding was confirmed by incubation of further sections with radiolabelled ligand and unlabelled VIP at a concentration of 1 μM. Autoradiograms were generated by exposure of the sections to LKB-Ultratfilm or emulsion coated glass coverslips. Areas of dense binding could be identified, correlating with the known actions of the peptide. For example, binding sites appeared to be dense in the smooth muscle and mucosa, in keeping with the peptide’s effects as a muscle relaxant and stimulator of water and electrolyte secretion. The methods described here open new opportunities for study of the anatomical distribution of peptide binding sites in the gut. They may be particularly useful in defining the pathogenesis of certain diseases.

Benzodiazepines stimulate duodenal epithelial bicarbonate secretion

J R HEYINGS, S E HAMPSOH, AND A GARNER (Bioscience Dept, ICI Pharmaceuticals Ltd, Alderley Park, Macclesfield, Cheshire) Gastrointestinal protective effects of benzodiazepines (BZ) in vivo are generally assumed to reflect a central action. We examined the influence of several BZ on duodenal HCO₃⁻ secretion, a process which protects the tissue from luminal H⁺ by generating a standing pH gradient at the mucosal surface. Bull frog proximal duodenum was stripped of seromuscular layers, mounted in a chamber and alkalisation of the unbuffered luminal bathing solution measured by continuous titration at pH 7.4 diazepam (1–100 μM, serosal side) induced a dose-dependent rise in luminal alkalisation and transmucosal potential difference (PD). Although some 500-times less potent than propranolol E, the increase in secretory rate was comparable to the PG-induced tissue maxima. Pretreatment with indomethacin (1 μM) had no effect whereas 2,4-dinitrophenol abolished the response to both agonists. Dose-related stimulation of alkaline secretion and PD was also observed with chlorodiazepoxide, nitrazepam, flunitrazepam and beta-carboline which increased secretion by 70%, 60%, 90%, and 55% respectively (all n=4) of the PGE₂ maximal response. These data show that BZ can act locally to stimulate electrogenic, energy dependent duodenal H⁺ secretion by a mechanism which is independent of endogenous PD production.

Preparation of osmotically active brush border membrane vesicles from biopsy samples of human small intestine

S P SHIRAZI-BEECHEY, A G DAVIES, AND R B BEECHEY (introduced by R M CASE) (Dept of Biochemistry, University College of Wales, Aberystwyth, Dyfed, and Bronlglas Hospital, Aberystwyth, Dyfed) The strategy has been to prepare and characterise in detail the brush border vesicles from different regions of the rabbit gut. This has been performed on a large scale. Brush border vesicles were then prepared from biopsy-sized portions of the rabbit gut. The properties of these vesicles were compared with those prepared on the large scale. No major differences were noted.

We have used the techniques that were developed with rabbit tissue, to prepare brush border vesicles from human jejunum and duodenum biopsy material. These vesicles have a characteristically high level of aminopeptidase N. They also have a Na⁺/dependent D-glucose transport system located within their membrane. This has a
very high activity, 1.6–3.4 nmol D-glucose transported/min mg protein. The transport is inhibited by phlorizin. The time course for the Na+-dependent uptake of D-glucose by these brush-border vesicles shows a transient accumulation, that is, typical overshoot behaviour. The level of accumulation of D-glucose shows that the transporter in human duodenum and jejunum is particularly active and that the movement of D-glucose through the membrane by passive, non-carrier mediated mechanisms is very low. These vesicles will enable the direct investigation of transport mechanisms in human intestinal tissues.

Induction of enteropathy by activated T cells in human small intestine

J T MACONALD AND J SPENCER (Paediatric Gastroenterology, St Bartholomew's Hospital and Department of Histopathology, University College, London) T cells in the lamina propria of explants of 16–22 week-old fetal human small intestine in organ culture were activated by adding pokeweed mitogen (PWM) to the culture medium. This resulted in the appearance of activated T cells (IL-2 receptor positive) in the lamina propria (but not the epithelium) and lymphokine secretion into the organ culture supernatant. Morphologically, explants stimulated with PWM developed villous atrophy and crypt hypertrophy after 72 hours in culture. There was also a dramatic increase in the number of dividing cells in the crypts, demonstrated immunochromically using the monoclonal antibody Ki67. Pokeweed mitogen only induced these changes in explants of fetal small intestine which contained T cells. Finally, the effects of PWM were inhibited by cyclosporin A. These results unequivocally show that activated T cells can produce a ‘cellie-like’ enteropathy in human small intestine and provide a model in which the mechanisms important in the development of enteropathy can be investigated.

Effect of rotavirus infection on water transport in infant mouse intestine in vitro

W G STARKY, J COLLINS, K J WORTON, T S WALLIS, G J CLARKE, J A SPENCER, S J HADDON, J STEPHEN, M P OSBORNE, AND D C A CANDY (Institute of Child Health, Department of Microbiology and Department of Physiology, University of Birmingham, Birmingham) An in vivo intestinal perfusion system was validated in order to study water and solute transport in infant mouse intestine, using 14C-polyethylene glycol as a non-absorbable water marker. Control small intestine, perfused with WHO oral rehydration solution (Na+ 90 mM, K 20 mM, HCO3 30 mM) with glucose replaced with mannitol, exhibited a mean (SEM; n) steady-state net water absorption over a period of 60 min of +10.6 ± 6 µl/cm/h (1.9 ± 0.7; n = 8). Absorption was inhibited at 4°C to mean net secretion of −0.7 ± 6 µl/cm/h (0.7; n = 8). Theophylline induced a mean net water secretion of −1.8 ± 6 µl/cm/h (0.5; n = 6). Mean recovery of 14C-PEG was 97%. Net water secretion was induced in mid-small intestines by rotavirus infection of 10 day old mice. Secretory rate was maximal at −5.3 ± 6 µl/cm/h (1.4; n = 7) 72 h postinfection, coinciding with the maximum severity of signs of diarrhoea and vacuolation of villous tip enterocytes. Peak ELISA titre of rotavirus antigen in intestinal tissue occurred at 48 h. Water secretion was reversed to net absorption (+5.4 ± 6 µl/cm/h (1.1; n = 6 p < 0.0005) by perfusion with WHO oral rehydration solution containing 111 mM glucose. This is in accordance with the clinical success of WHO oral rehydration solution in humans with rotavirus diarrhoea. Water absorption in the upper small intestine and colon was not significantly altered by rotavirus infection.

Inhibition of ethanol induced leukotriene synthesis and damage in the rat gastric mucosa by BW755C

N K BOUGHTON-SMITH and B J R WHITTLE (Department of Mediator Pharmacology, Wellcome Research Laboratories, Beckenham, Kent) Oral administration of ethanol induces damage and increases pro-inflammatory leukotriene (LT) release from the rat gastric mucosa. Using the lipoxigenase inhibitor, BW755C, the relationship between LT release and ethanol induced damage was further investigated.

Fasted rats (male, 180–200 g) were pretreated with BW755C (5–50 mg/kg po) or vehicle, 30 min before oral absolute ethanol (1 ml). After 5 min, the gastric damage was assessed planimetrically and the mucosal formation of cicosanoids, from chopped mucosa incubated for 20 min at 37°C, determined by specific radioimmunoassays.

Immunoreactive LTβ and LTc release by the control gastric mucosa (5 ± 2 ± 0.5 ng/g and 81 ± 27 ± 8 ng/g of tissue respectively, mean ± SEM n = 5) was increased after ethanol (to 21 ± 2 ng/g and 164 ± 14 ng/g of tissue respectively, n = 5; p < 0.05). Ethanol induced damage, which involved 30 ± 4% (n = 6) of the total mucosal area was reduced (p < 0.05) by BW755C at doses of 20 mg/kg and 50 mg/kg (42 ± 13% and 63 ± 12% inhibition respectively), as was the mucosal formation of LTβ (79 ± 4% and 78 ± 7% inhibition respectively, p < 0.01) and LTC4 (92 ± 2% inhibition at 20 mg/kg, p < 0.01). The formation of 6-keto-PGF1α was unaffected by BW755C.

BW755C thus inhibits both ethanol induced gastric mucosal damage and the increased formation of LTβ and LTC4, but did not affect formation of the mucosal prostanooids. The failure of BW755C to prevent completely the ethanol induced damage when there was near-maximal inhibition of LT synthesis may indicate that additional mechanisms are involved in its protective action.

Acute intestinal ischaemia: differential response of gut neuropeptides

J. MELEAGROS, J S GILL, P. K MULDERY, J. DOMIN, M. GHATI, AND S. R. BLOOM (Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London) Superior mesenteric artery (SMA) occlusion is a life threatening condition associated with complex pathophysiological disturbances locally and systemically. We have investigated the response of certain gut neuropeptides in experimental SMA occlusion in the anaesthetised rat. The SMA was clamped at its origin for five (n = 10) or 20 (n = 10) minutes. After release of the clamp, blood samples were taken by aortic puncture and all the areas of the gut were extracted in boiling 0.5 M acetic acid. Neuropeptides in plasma and tissues were measured by specific radioimmunoassays. Results, analysed by ANOVA, revealed a rise in plasma calcitonin gene related peptide (CGRP); controls (n = 10) 65 ± 10, five minute ischaemia 106 ± 16 (NS), 20 minute 147 ± 36 (p < 0.05) (mean ± SEM pmol/l) but not in plasma neuropeptide Y (NPY). In the gut jejunal CGRP fell from 31 ± 1 ± 6 to 23.8 ± 1 ± 5 (p < 0.05) and to 22.1 ± 1 ± 5 (p < 0.01) and substance P from 70 ± 5 to 46 ± 2 (p < 0.01) and to 51 ± 3 (p < 0.05) after 5 and 20 minutes of ischaemia (mean ± SEM pmol/l) reflecting local release. Ileal and right colon concentrations fell but not significantly. In contrast NPY and bombesin concentrations were unaltered. Therefore in acute ischaemia the vasodilatory neuropeptides CGRP and substance P, but not the vasoconstrictors NPY.
and bombesin, are released locally suggesting possible mechanisms that may operate to limit the extent of ischaemic damage.

Electrophoretic analysis of microvillus membranes in coeliac disease

P W PEMBERTON, R W LORLEY, AND R HOLMES (University Department of Gastroenterology, Manchester Royal Infirmary, Oxford Road, Manchester) We have previously described a technique for analysing microgram amounts of intestinal microvillus membranes by two dimensional electrophoresis (protein mapping) and used it to determine the protein composition of normal human membranes. We have now applied the technique to the analysis of the membrane in coeliac disease.

Jejunal biopsies were obtained from controls, and from coeliac patients in relapse and remission. Microvillus membranes were isolated by the Ca\(^{2+}\) precipitation method, solubilised in 2% SDS and radio-labelled with \(^{3} \)H by reductive methylation before electrophoresis. One dimensional separation was performed by conventional SDS-polyacrylamide gel electrophoresis while two-dimensional analysis was by isoelectric focussing followed by SDS-PAGE. Proteins were detected by fluorography of the dried gels and glycoproteins by lectin-affinity staining of Western blots.

Compared with controls, the protein map in untreated coeliac disease was grossly abnormal. Numerous high M\(_{r}\) proteins, including the brush border enzymes and other glycoproteins were absent, while smaller proteins - for example, actin, were unaffected. After treatment, the protein map returned essentially to normal with restoration of the high M\(_{r}\) proteins, and no specific abnormality of the coeliac microvillus membrane could be identified.

Acetate uptake in rat small intestine is not sodium dependent

A J M WATSON, P A LEAR, E J ELLIOTT, R F M WOOD, AND M J G FARTHING (Dept of Gastroenterology and Surgery, St Bartholomew’s Hospital, London) We have previously shown that in successful rat small bowel transplants impaired water absorption cannot be accounted for by mucosal damage. To determine the cause of this reduction water absorption was studied in allografts (n=10) and compared with (1) Thiry-Vella (TV) loops (n=10), (2) isografts (n=6), (3) denervated TV loops (n=5), and (4) ischaemic TV loops (n=4) using a steady state perfusion technique of isotonic 30 mM glucose-osmolaline nine days after transplantation. All animals were treated with an identical dose of cyclosporin A (15 mg/kg for seven days only). Water absorption was reduced by 55% in allografts compared with TV loop controls. This was not because of rejection as there was a similar reduction in isografts (median 42.6, range (17.5-77.7) v allografts (median 39.0, range (19.6-54.2) \(\mu\)l/min/g, respectively). When TV loops were denervated, however, water absorption was reduced to levels found in allografts (median 26.0, range (8.7-48.0). Water absorption was not reduced in ischaemic TV loops. In contrast, no difference was found in glucose absorption between allografts and the other control groups studied, suggesting villus absorptive function remains intact. We conclude that the reduction of water absorption in successful small bowel transplants is primarily caused by denervation rather than rejection or ischaemia.

Segmental variability of electrogenic Na\(^{+}\) transport in human colon

G I SANDLE AND F MCGLOINE (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) Electrogenic Na\(^{+}\) transport is present in normal human distal colon and is enhanced by aldosterone. The Na\(^{+}\) channel blocker amiloride markedly inhibits basal electrogenic Na\(^{+}\) transport in human distal colon but has considerably less effect in human proximal colon. To further study the basis for this segmental difference in amiloride sensitivity, the effects of amiloride (10 \(^{-3}\) M) and Na\(^{+}\) replacement with choline were determined in proximal (ascending) and distal (sigmoid/proximal rectum) colon resected from patients with cancer or diverticular disease. In NaCl Ringer, basal electrical properties of proximal (n=9) and distal colon (n=8) were similar, and the mucosal addition of amiloride decreased short circuit current (Isc) by 147±32 \(\mu\)A/cm\(^2\) (p<0.005) and total conductance (G\(_{T}\)) by 1.6±0.6 mS/cm\(^2\) (p<0.05) in distal colon, but only decreased Isc by 47±13 \(\mu\)A/cm\(^2\) (p<0.01) and G\(_{T}\) by 1.2±0.4 mS/cm\(^2\) (p<0.05) in proximal colon. In choline CI Ringer, Isc decreased almost to zero in both colonic segments, suggesting that electrogenic Na\(^{+}\) transport was present equally in the proximal and distal colon. Kinetic studies on the basolateral Na\(^{+}\)-K\(^{+}\) pump revealed that the maximum pump activity, pump affinity for Na\(^{+}\), and the number of Na\(^{+}\) ions binding to each pump site, were similar in the proximal and distal segments. Thus, short circuit current throughout human colon is Na\(^{+}\)-dependent and probably reflects an electrogenic Na\(^{+}\) transport process which is amiloride-sensitive only in the distal segment. This segmental variability in amiloride sensitivity may reflect a segmental difference in mucosal responsiveness to aldosterone.

Differential effects of pure mineralocorticoid and glucocorticoid hormones on colonic Na\(^{+}\) and K\(^{+}\) transport

G I SANDLE AND F MCGLOINE (Department of Medicine, Hope Hospital (University of
The glucocorticoid dexamethasone binds to glucocorticoid and mineralocorticoid receptors in mammalian colon, and stimulates electrogenic Na+ transport. K+ secretion and mucosal Na+/K+-ATPase activity, but it is unclear which type of receptor is more important in mediating these changes. We therefore used microelectrodes in vitro to compare the effects of hyperaldosteronism (secondary to dietary Na+ depletion) and a pure glucocorticoid (RU 28362, Roussel; 600 μg/100 g BW/day for three days) which has no affinity for mineralocorticoid receptors, on Na+ and K+ transport in rat distal colon. Compared with control tissues, aldosterone increased transepithelial voltage five-fold (p<0.001), total conductance 2.3-fold (p<0.001), hyperpolarised the basolateral membrane by 11 mV (p<0.025), and decreased the apical/basolateral membrane resistance ratio by 64% (p<0.01). In contrast, RU 28362 increased transepithelial voltage three-fold (p<0.001), had no effect on total conductance or basolateral membrane voltage, and decreased apical/basolateral membrane resistance ratio by 60% (p<0.01). Studies with specific ion channel blockers indicated that both aldosterone and RU 28362 induced appreciable Na+ and K+ conductances in the apical membrane. Kinetic studies of the basolateral Na+K+ pump revealed that aldosterone increased maximum pump activity by 230% (p<0.001), but RU 28362 decreased maximum pump activity by 45% (p<0.01). Thus, aldosterone and RU 28362 both enhance apical membrane conductance to Na+ and K+, but have opposite effects on the basolateral Na+K+ pump. The transport effects of dexamethasone are therefore likely to mainly reflect activation of mineralocorticoid receptors.

Mechanism of laxative action of phenolphthalein of intestinal fluid absorption

ANDREA J PHILLIPS AND HELEN L LEATHARD (Department of Pharmacology, Charing Cross and Westminster Medical School, London) The action of phenolphthalein on intestinal fluid transport was investigated, on rat everted intestinal sacs, by adding drugs to the fluid bathing the mucosal surface. Phenolphthalein (3.1×10−5 M) reduced net fluid absorption in the small intestine (p<0.05, n=25), but not in the colon (p>0.05, n=7). The former effect was antagonised by tetrodotoxin (3.1×10−5 M, p<0.05, n=10), indicating the involvement of a nervous mechanism. Atropine (3.5×10−6 M) partially antagonised phenolphthalein whilst abolishing basal secretion (p<0.05, n=9), showing that cholinergic and non-cholinergic secretory nerves may be involved. In the presence of atropine, imitation of the effects of phenolphthalein by carbachol (1.1×10−5 M) suggests that activation of neuronal cholinergic receptors promotes the release of a non-cholinergic secretory neurotransmitter. Apamin (5×10−6 M), which had no effect on basal secretory activity (p>0.05, n=9), completely inhibited phenolphthalein (p<0.05, n=8). As apamin has been reported to inhibit neural release of vasoactive intestinal polypeptide (VIP), this suggests a role for VIP as the non-cholinergic secretory neurotransmitter. It is concluded that the laxative action of phenolphthalein is partially mediated by inhibition of small intestinal fluid absorption via a nervous pathway. This appears to involve cholinergic activation of a VIP-ergic nerve.

Lung permeability in inflammatory bowel disease (IBD) and coeliac disease (CD)

D A F ROBERTSON, H SIDHU, N TAYLOR, A BRITTEN, C I SMITH, AND G HOLDSTOCK (Depts of Medicine and Nuclear Medicine, Southampton General Hospital, Southampton) Respiratory disease and subclinical pulmonary abnormalities have been identified as complications of both CD and IBD, but the pathogenesis of the lung disease remains uncertain. Possible explanations include a common mucosal permeability defect allowing absorption of antigens with subsequent damaging tissue reactions, both in gut and lung, or exposure to an environmental agent causing both lesions, immune complex deposition or pulmonary vasculitis.

We have studied lung function including permeability measured by clearance of inhaled 99Tc-DTPA (expressed as time for ½ inhaled 99Tc-DTPA to clear from lungs to blood: t½ in 25 IBD and 18 CD patients on a gluten free diet, and in 20 controls, all without respiratory symptoms. In IBD there was evidence of obstruction to airflow (mean FEV1/FVC = 75.8%, control 81% p<0.05) but no change in pulmonary permeability (t½ = 70.3 mins v 69.2). In CD airflow was not significantly different from control (FEV1/FVC = 80%) but there was an increase in pulmonary permeability (t½ = 48.9 min; p<0.01). These findings suggest that the mechanism of lung disease in CD differs from that in IBD, and supports the hypothesis of a common mucosal defect in lung and jejunum in CD allowing increased permeability.

Mucosal cell receptors and enteric nerves mediate the spasmodic effects of bacterial N-formyl oligopeptides on guinea pig ileum

VI S CHADWICK, C H HOBSON, AND M F BROOK (Wellcome Medical Research Institute, University of Otago Medical School, PO Box 913, Dunedin, New Zealand) The mechanism of the intestinal spasmodic action of bacterial N-formyl (methionyl) oligopeptides has not been defined. We have determined pA2 values for eight potential antagonists (receptor, nerve or ganglion blockers) of the formylated polypeptide (FMLP) using histamine, acetylcholine, nicotine, SHT and Substance P as control agonists. A synthetic FITC-labelled peptide and a rhodamine labelled anti-FITC antibody were used to identify receptors for bacterial peptides in ileal mucosa.

Atropine (pA2=8.4), pirenzepine (8.0) and tetrodotoxin (7.9) were potent antagonists of FMLP induced contraction suggesting involvement of M2 cholinergic neural pathways which modulate slow excitatory post-synaptic potentials in the enteric nervous system. Tachyphylaxis experiments demonstrated that SHT and Substance P receptors were not involved. Salazopyrine, known to block FMLP receptors on neutrophil leucocytes also antagonised FMLP responses (pA2=7.3). FITC-labelled peptide was bound and internalised by granulated cells in ileal mucosa and removal of mucosa from ileal segments abolished muscle responses to FMLP but not to histamine or acetylcholine.

We conclude that bacterial N-formyl peptides, produced by many intestinal bacteria bind to cells bearing receptors in ileal mucosa and produce muscle contraction via enteric neural pathways.

Enprostil – an advance in gastric ulcer therapy?

A G MORGAN, C PACSOO, P TAYLOR, AND W A F MACGADAM (Endoscopy Unit, Airedale General Hospital, Steeton, Keighley, Yorks) In a random double blind endoscopically controlled study, 100 patients with gastric ulcers were treated with either enprostil (70
Esaprazole increases gastric alkaline secretion in man

M Guslandi (Istituto di Medicina Interna, Milano, Italy) Esaprazole, N-[N-(cyclohexyl-carbamoyl)methyl] piperazine hydrochloride, is a novel antiulcer compound reportedly as effective as cimetidine in the short term treatment of peptic ulcer.

The drug, which has a low antisecretory activity, was found to exert cytotoxic effects against various necrotising agents. In order to further elucidate the mechanism of action of esaprazole, the effect of the drug on gastric bicarbonate secretion has been investigated in man. Twelve healthy volunteers, 10 men and two women, aged 18-56 years, entered the study after giving informed consent. They were treated with esaprazole by oral route at a dose of 1350 mg daily for 10 days.

Before and after treatment basal bicarbonate secretion in fasting gastric juice was determined by means of Feldman's method, on the basis of H⁺ concentration, secretory volumes, osmolality of gastric juice and plasma. A highly significant increase (p<0.01) in gastric HCO₃⁻ secretion, from 2.65±0.57 (mean±SD) to 4.28±0.79 mmol/l was observed after esaprazole treatment, this effect being detectable in all subjects.

Gastric HCO₃⁻ ions are known to contribute to mucosal protection by neutralising back-diffusing H⁺ ions within the mucus layer. Strengthening of the gastric mucus bicarbonate barrier by esaprazole may partially account for the cytoprotective and ulcer-healing properties of this new therapeutic agent.

Colloidal bismuth subcitrate (DE-NOL) in non-ulcer dyspepsia. Placebo controlled trial with particular reference to the role of Campylobacter pyloridis

T Rokkas, C Pursey, N A Simmons, M J Hlpe, and G E Sladen (Gastroenterology Unit, Div of Medicine, Dept of Clinical Bacteriology and Histopathology, UMDS Guy's and St Thomas' Hospitals, London) Fifty patients (35 M, 15 F, mean age 39-5 years, range 20-60 years) with NUD and no recent history of NSAID consumption, were studied to evaluate the effect of DE-NOL on symptoms and on infection with C pyloridis. All patients had normal abdominal US and in all gastroscopy revealed no significant GI pathology. Patients were allocated randomly to eight weeks treatment with either placebo or DE-NOL after which they were re-evaluated clinically and endoscopically. Antral biopsies were examined bacteriologically and histologically.

Patients on placebo and DE-NOL did not differ regarding sex, age, smoking, alcohol consumption and C pyloridis +ve cultures (11/25 in DE-NOL and 8/25 in placebo group). All 19 C pyloridis +ve patients (100%) had active gastritis in contrast with only eight (19.3%) of C pyloridis -ve patients (p<0.001). DE-NOL eradicated C pyloridis from 9 (81.8%) of the 11 +ve patients compared with placebo which did not eradicate C pyloridis from any of the eight +ve patients (p<0.01). In patients receiving DE-NOL, compared with placebo, the gastritis (p<0.01) and the symptoms (p<0.001) improved.

We conclude that DE-NOL is effective in NUD and this is associated with eradication of C pyloridis from the stomach.
mucosa (pg/mg WW/20 min, means±SEM) 1198±157±4 and 887±102±3 (p<0.02), whereas release of LTC4 was significantly higher in duodenal than antral mucosa, 96±18±1 and 56±12±2 (p<0.01). Ionophore stimulated LTC4 generation was significantly increased (duodenum 183±24±3, p<0.01; antrum - 89±20±2, p<0.05), but not the release of PGE2 (duodenum - 278±111±7 (p<0.001); antrum 329±86±8 (p<0.001) suggested a different cellular origin for the two eicosanoids. Ulcer healing after CBS therapy did not alter basal PGE2 and LTC4 generation either in duodenal or antral mucosa, but stimulated LTC4 formation was significantly reduced (p<0.001).

These results suggest that LT formation may be of greater significance than PG synthesis in duodenal ulcer disease.

A single blind comparative study of misoprostol to sucralfate and placebo in the prevention of aspirin induced ulceration

F LANZA, K E PEACE, I GUSTITUS, AND B DICKSON (Baylor College of Medicine, Houston, Tx and G D Searle Skokie, Ill, USA) We report for the first time, the results of a direct comparison of the cytoprotective properties of misoprostol (M) to sucralfate (S) and to placebo (P) in normal subjects taking aspirin (A).

Thirty healthy volunteers with endoscopically normal gastroduodenal mucosa were randomised into three equal groups to receive M 200 μg, S 1 g. or P, co-administered with A 650 mg four times daily for seven days. After a single final dose on day seven, endoscopies were carried out and the mucosa were graded in a blinded fashion according to a 0–4+ scale: 0 = normal; 1+ = single hemorrhage or erosion; 2+ = 2 to 10 haemorrhages or erosions; 3+ = 11 to 25 haemorrhages or erosions; and 4+ = more than 25 haemorrhages or erosions or an invasive ulcer of any size.

Utilising a score of 2+ or less as a clinically significant prophylactic success, the success rates were: M 10/10 (100%), S 2/10 (20%), and P 0/10 (0%). Misoprostol was statistically superior to S (p=0.0001) and to P (p=0.00001). Ninety five per cent confidence intervals on the difference in success rates between M and S and M and P were (44%: 100%) and (61%, 100%) respectively. Adverse experiences were minor and comparable across treatment groups.

Succralfate (SUC) v cimetidine (CIM) for the treatment of duodenal ulcer (DU) associated antral gastritis

W M HUI, S K LAM, J HIO, C L LAI, A FLOK, M M T NG, AND T LUI (Departments of Medicine and Pathology, University of Hong Kong, Queen Mary Hospital, Hong Kong) Antral gastritis is closely associated with DU and improves with DU healing and treatment with misoprostol. We conducted a single blind, randomised study to compare the therapeutic effect of CIM, an acid inhibitory agent (200 mg tds and 400 mg noxite) and SUC. a site protective agent (1 g qid) on antral gastritis associated with active DU. two antral and two funal gastric biopsies were taken endoscopically before and after treatment. The activity of the gastritis as assessed histologically by the infiltration of polymorphs was graded blindly by two pathologists as nil, mild, moderate or severe. The two groups (CIM n=71, SUC n=69) were comparable in their clinical characteristics. Despite similar rates of DU healing in the two groups (75%, 78% at four weeks) the incidence of improvement of activity of antral gastritis (nil or mild as endpoint) was significantly higher in the SUC (33%-3%) than in the CIM (18%-3%) group (p<0.05) and in the healed DU group the improvement was significantly higher in the SUC (36-4%) than CIM (16-4%) group (p<0.02). Smoking did not affect the improvement in both groups. During the subsequent 24 month follow up ulcer recurrence rate in the CIM group was double that in the SUC group.

We conclude that histological improvement of the activity of DU associated antral gastritis was significantly higher with sucralfate than with cimetidine treatment despite similar healing rate.

Does the pH influence the protective action of sucralfate against mucosal injury?

B J Z DANESIL, A DUNCAN, AND R E RUSSELL (Gastroenterology Unit, The Royal Infirmary, Glasgow) An acid medium is claimed to be mandatory for the mucosal protective action of sucralfate. In situations where acid secretion is inhibited the efficacy of this drug to protect against mucosal injury has, therefore, been questioned. We examined the effect of sucralfate on mucosal erosions induced in rats (n=200) by aspirin (PKa 3-5) and bile acids (taurodeoxycholic and taurocholic acids: PKa 1-8, and glycocholic acid: PKa 3-9) at pHs 1-5 and 6-5. We also studied the effect of sucralfate on the intragastric pH (using a pH microelectrode), on absorption of salicylate and on peptic activity. These parameters were examined four hours after oral administration of test solutions. Sucralfate significantly reduced the incidence and severity of mucosal erosions (p<0.001) induced by aspirin alone and when combined with the three bile acids at both pHs of 1-5 and 6-5. Rats which received sucralfate had a higher (p<0.001) intragastric pH than those which did not receive this drug. Sucralfate did not influence salicylate absorption or peptic activity. We have shown that the protective effect of sucralfate against mucosal injury induced by aspirin and bile acids is not pH dependent. The simultaneous use of drugs which inhibit acid secretion, thus, may not reduce the protective efficacy of this drug. Stimulation of alkaline production may play a role but inhibition of pepsin and binding of aspirin to sucralfate are unlikely to be factors in the mechanism of sucralfates action.

Effect of treatment with famotidine on T-lymphocyte populations and activity in duodenal ulcer patients

R MOUNTFORD, A W PREECE, R JONES, E GROVE, AND J COTTRELL (University Department of Medicine and Oncology Research Unit, Bristol Royal Infirmary, M50 Limited, Hoddesdon, Herts) Cimetidine has been reported to stimulate cell mediated immunity, possibly through interaction with suppressor cell H2-receptors; such effects could contribute to ulcer healing with H2-antagonists. We have studied the effects of famotidine, an H2-antagonist structurally different from cimetidine, on T-cell populations in duodenal ulcer patients. Lymphocytes were isolated from blood samples of 20 patients, before and during treatment with famotidine 40 mg nocte, and one untreated control group of non-ulcer patients (n=19) and healthy volunteers (n=6). Mean pretreatment values for T-cell (pan-T) percentages and helper/suppressor ratios estimated using monoclonal anti-body labelling, did not vary significantly from control groups (64±12% and 1-97±0-79:1 v 55±13% and 2-04±0-99 non-ulcer controls, 56±13% and 1-5±0-76:1 healthy controls) or during treatment: three days - 63±13% and 2-0±0-75:1; two weeks - 64±11% and 1-82±0-8:1; six weeks - 58±29% and 1-84±0-53:1. Mean pretreatment Con-A stimulated lymphopoeic production, estimated by reduction of macrophage electrophoretic mobility, was also

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similar to control values (13±4% v non-ulcer controls 12±5%, healthy controls 8±3%) and did not vary significantly during treatment: three days – 13±6%; two weeks – 13±6%, six weeks 11±5%. In conclusion famotidine does not modify T-lymphocyte populations or lymphokine production in duodenal ulcer patients. Immunomodulation by cimetidine may be due to molecular rather than H2-mediated effects.

24 hour intragastric acidity and plasma gastrin concentration in healthy volunteers taking famotidine 40 mg noce

S LANZON-MILLER, R F POUNDER, S G BALL, D J DAIGLEISH, J COWARD, AND A O JACKSON (Royal Free Hospital School of Medicine, London) Famotidine is a new H2-receptor antagonist. This study compared the effects on 24 h intragastric acidity and plasma gastrin concentration of the 7th day of treatment with either famotidine 40 mg or placebo, taken as a tablet at 2100 h. The treatment was given in a predetermined random order. Ten healthy volunteers took part in the study: median age 22 years, median weight 72 kg.

Median integrated 24 h intragastric acidity fell from 666 pmol/h/l on placebo to 281 pmol/h/l on famotidine 40 mg noce. Conversely, median integrated 24 h plasma gastrin concentration rose from 248 to 394 pmol/l on treatment with famotidine. Both of these changes are significant (p<0.001).

Analysis of the data by 'meal-related intervals' shows that the decrease of intragastric acidity during treatment with famotidine is due entirely to a decrease of nocturnal acidity – daytime acidity is unaffected by the drug. Famotidine 40 mg noce causes a significant increase of plasma gastrin concentration during the night, morning and afternoon, with no effect in the evening.

Famotidine 40 mg noce causes a significant decrease of nocturnal acidity, with a longer lasting rise of plasma gastrin concentration.

Optimising the effect of nizatidine on gastric pH: early evening meal together with the drug is best

P DURoux, P BAuerFEND, C EMDE, H R KOELz, D MARGalIth, G DORTA, A KARPE, P P KEOHANe, AND A L BLUM (Gastroenterology CHUV-Lausanne and Stadtspital Triemli, Zurich, Switzerland, Lilly-England) In our previous studies H2-antagonists were more effective after early evening intake than after late intake. The question arises whether the meal interacts with the drug. We thus conducted a randomised double-blind placebo controlled crossover study. In each of 12 healthy volunteers six ambulatory 24-h pH-metries (glass electrode in the gastric corpus, 30 samples/minute, start at 4 pm) were performed. Drug serum concentrations were determined in the first four hours. The following six treatments were randomised: N6/D6 (nizatidine 300 mg at 6 pm and dinner at 6 pm), N9/D6 (nizatidine 300 mg at 9 pm and dinner at 6 pm), N6/D9, N9/D9, P/D6 (placebo, dinner at 6 pm) and P/D9, respectively. pH-median were calculated from 6 pm to 12 pm (evening), from 6 pm to 7 am (night) and from 7 am to 12 am (morning).

In the evening period pH-values were higher with N6 than with P (mean of pH-median: N6/D6 3-5 v P/D6 1-4; N6/D9 3-9 v P/D9 1-6); N9 was not different from P; N9/D6 was inferior to N6 (N9/D6 1-7 v N6/D6 3-9 and N6/D6 3-5). During the night N6 and N9 were superior to P (N6/D6 3-8 and N9/D6 3-6 v P/D6 1-9; N6/D9 3-3 and N9/D9 3-5 v P/D9 1-5) (p<0.01 multiple comparisons by Wilcoxon/Wilcoxon). The effect of nizatidine ceased with breakfast. Drug serum concentration peaked ±120 minutes earlier when nizatidine was taken without meal than when nizatidine and meal were taken together.

We conclude that (1) A concomitant meal slows the absorption of nizatidine and may thus prolong its action. (2) Nizatidine is most effective when given at 6 pm together with a meal. Supported by SNF 3.827.0.86 and DFG E 361/1-3.

Dose dependent inhibition of twenty four hour intragastric acidity by WY-45,727 a new potent H2-receptor antagonist

H MERKl, L WITZEL, J NEWMANN, D KAUfMANn, AND J ROEHMEL (INTRODUCED BY R P WALT) (DRK Hospital, West Berlin, FRG) WY-45,727 (Wyth Labs) is a new furan H2-receptor antagonist of greater potency than ranitidine (3-10X). We measured the effects of increasing doses of WY-45,727 (20 mg, 50 mg, 150 mg) on 24 hour intragastric acidity in 20 normal volunteers in random order under double blind conditions. pH was measured continuously by intragastric glass electrodes and each volunteer underwent four identical studies. Medication was taken after supper at 1830 h. Statistical analysis to assess the hypothesis that increasing doses would produce increasing suppression of acidity was by the non-parametric PAGE test for order effects. Median nocturnal pH rose from 1-3 (placebo) to 2-4 (92% decrease of acidity), 6-0 (99% decrease), and 6-7 (99% decrease) with increasing doses of WY-45,727. Antisercretory effects during the day were limited; 21%, 37%, and 75% decreases respectively. Overall 24 hour median pH rose from 1-3 (placebo) to 1-9, 3-1, and 4-5 with 20 mg, 40 mg, and 150 mg respectively. Clear dose dependent decreasing acidity was confirmed (p<0.001) and effects were greatest at night. Such potent suppression of gastric acidity should make WY-45,727 an effective ulcer therapeutic agent worthy of further study.

Effect of intravenous BMY-25368-01 (BMY) and ranitidine (R) on meal stimulated gastric acid secretion in man

H G DAMMANN, F BURKHARDT, P MULLER, R SMON, R CRENSHAW, K MANGHANI, AND S SCHWARTZ (Krankenhaus Bethanien, Hamburg, FRG, and Pharmaceutical Research and Development Division, Bristol-Myers Co, Wallingford, USA) In this blinded (BMY doses v placebo), randomised, crossover study, a single iv dose of BMY (1-amin0-2-3-piperidinomethylphenoxy propylaminol cyclohut-l-cne-3,4-dione hydrochloride), an inherently long acting and novel histamine H2-receptor antagonist, 50 mg of R, or placebo was administered to healthy volunteers. BMY was studied at 5, 12-5, and 25 mg. Subjects received either BMY and placebo or R and placebo. Six subjects were in each group except the BMY-5 mg group that consisted of five subjects. Medications were administered at 0700 hours, and uniform homogenised meals (standardised to pH 5) were administered at 0800, 1300, and 1800 hours. Volunteers receiving 25 mg of BMY were administered a 4th meal at 0500 hours of the subsequent day. Gastric acid secretion was determined using an automatic titrator that maintained the intragastric pH at 5 for two hours after administration of each meal. No untoward clinical effects were observed with either RMY or BMY. Intravenous BMY is more potent than and longer acting than R. A single iv dose of 25 mg of BMY produces significant inhibition of meal stimulated gastric acid secretion for 24 hours. Intravenous BMY is a OD antisecretory agent.
Omeprazole improves antral gastritis associated with duodenal ulcer (DU)

W M HUI, S K LAM, J HO, L LUI, W Y LAU, F J BRANICKI, C L LAI, A S F LOK, AND M M T NG (Departments of Medicine, Surgery and Pathology, University of Hong Kong, and Government Surgical Unit, Queen Mary Hospital, Hong Kong) Antral gastritis occurs in close to 100% of patients with active DU. Whether gastric acid secretion plays a pathogenetic role in antral gastritis is unknown. We carried out a double blind randomised trial comparing omeprazole (OME) 10 mg OM, 20 mg OM and ranitidine (RAN) 150 mg bd in 270 patients with active DU. Healing of the ulcer was assessed weekly by endoscopy with at least two antral biopsies taken to assess the activity and degree of chronic inflammation histologically by the degree of polymorph and mononuclear cell infiltration respectively and graded blind by two pathologists as nil, mild, moderate and severe. The sex, age and maximal acid output were comparable in the three groups. DU healing at two weeks was 77%, 86%, and 63% respectively, while that at four weeks was 95%, 96%, and 93% respectively. The percentage of patients with improvement in the activity of gastritis in the four consecutive weeks was 9%, 40%, 51%, and 53% for OME 10 mg (n=78), 14%, 42%, 49%, and 53% for OME 20 mg (n=81) and 2%, 23%, 30%, and 33% for RAN (n=82), and life table analysis: OME 10 mg v RAN and OME 20 mg v RAN; p<0.01. The degree of chronic inflammation showed similar changes. Gastric acid and smoking did not affect the improvement of gastritis. Thus despite similar DU healing rates at four weeks, OME 10 or 20 mg daily is significantly better than ranitidine 150 mg bd in improving antral gastritis, suggesting that intense acid inhibition helps to improve the antral gastritis.

Omeprazole (OME) v ranitidine (RAN) for duodenal ulcer – weekly endoscopic assessment

W M HUI, S K LAM, W Y LAU, F J BRANICKI, C L LAI, A S F LOK, M M T NG, K P POON, AND P J FOK (Departments of Medicine and Surgery, University of Hong Kong, and Government Surgical Unit, Queen Mary Hospital, Hong Kong) To investigate the DU healing efficacy of two to four weeks' treatment of OME. 270 Chinese patients with endoscopically active DU were randomised to a double blind controlled trial of OME 10 mg daily (low dose), 20 mg daily (standard dose) and RAN 150 mg bd. Forty six potential factors affecting healing including clinical and endoscopic characteristics were prospectively obtained and healing was assessed by endoscopy at weekly intervals for at least two weeks and up to four weeks if DU remained unhealed. The cumulative healing rates per protocol analysis in the consecutive four weeks were 43%, 77%, 94%, and 95% for OME 10 mg (n=83), 49%, 86%, 93%, and 96% for OME 20 mg (n=87) and 29%, 63%, 83%, and 93% for RAN (n=84) respectively. (Life table analysis OME 10 mg v RAN, p<0.01, OME 20 mg v RAN p<0.001.) There was a trend towards more rapid symptoms relief with OME, particularly nocturnal pain during the first week. In the omeprazole treated group (combined 10 and 20 mg) healing rate is lower in the smoker than non-smoker (p<0.0008), early than late onset (symptoms before and after age 30 years respectively, p<0.02), remission >5 v <5 months (p<0.05) and high acid v normal (p<0.05) by life table analysis. We conclude OME 10 mg achieved similar healing rates as OME 20 mg and both resulted in significantly better healing rates than RAN. Smoking, short remission period, early onset and high acid secretion adversely affected healing.

Omeprazole and ranitidine in the treatment of benign gastric ulcer – an international multicentre study

A WALAN, J P BADER, M CLASSEN, C B H W LAMERS, D W PIPER, AND R RUTGERSSON (Linköping, Sweden; Créteil, France; Munich, FRG; Leiden, Netherlands; Sydney, Australia; Malmö, Sweden) The aims of this international multicentre study were to study the ulcer healing and tolerability of four to eight weeks' treatment with omeprazole 20 mg once daily (om), omeprazole 40 mg om and ranitidine 150 mg twice daily (bd) in patients with gastric and prepyloric ulcers. Forty five centres in 13 countries contributed a total of 602 patients of whom 203 received omeprazole 20 mg, 194 omeprazole 40 mg, and 205 ranitidine. At four weeks, 59% of patients in the ranitidine group were healed compared with 69% of the omeprazole 20 mg group and 80% of the omeprazole 40 mg group. At eight weeks, the corresponding figures were 85%, 89%, and 96%, respectively. The healing rates were significantly higher with omeprazole 40 mg both at four and eight weeks compared with ranitidine (p=0.001) and omeprazole 20 mg (p=0.02). After adjustment for an imbalance at entry in terms of more patients with larger ulcers in the omeprazole 20 mg group, both omeprazole groups produced significantly higher healing rates at four weeks compared with ranitidine (omeprazole 20 mg v ranitidine p=0.001, omeprazole 40 mg v ranitidine p<0.0005). There was a more pronounced improvement in ulcer symptoms during the first two weeks in the omeprazole groups. A significant difference was shown between omeprazole 40 mg and ranitidine (p=0.02). All treatments were well tolerated and there was no difference in the prevalence of adverse events between the three groups.

In conclusion, omeprazole 20 mg and 40 mg om have been shown to be superior to ranitidine 150 mg bd in promoting healing of gastric and prepyloric ulcers, and there was a better symptom relief with omeprazole 40 mg.

Effect of omeprazole on postprandial gastric and duodenal pH in exocrine pancreatic insufficiency

G MCLAUCHLAN, G P CREAN, AND K E L MCCOLL (University Department of Medicine, Western Infirmary and Gastrointestinal Centre, Southern General Hospital, Glasgow) In exocrine pancreatic insufficiency duodenal acidity (pH<4) may inactivate residual endogenous enzymes and gastric acidity destroy oral pancreatic supplements. The effect of omeprazole on gastric and duodenal pH has been studied in six patients with steatorrhoea caused by chronic pancreatitis. Combined glass electrodes (Radiometer GK2801C) were positioned in the second part duodenum and body of stomach and 24 h ambulatory pH measured after seven days on omeprazole 40 mg/day, omeprazole 20 mg/day and placebo given double blind in random order with two week washout periods. The drugs were taken orally at 0800 h and the two three hours postprandial periods after the midday and evening meals were combined and analysed. The percentage of the postprandial period that gastric pH was below 4 ranged from 58%–100% on placebo; on omeprazole 20 mg it was 0% in three patients and 42%, 68%, and 86% in remainder and on omeprazole 40 mg it was 0% in five patients and 76% in one. In the duodenum, the percentage postprandial time that pH was below 4 on placebo was 0% in three patients and 13%, 15%, and 26% in others, on omeprazole 20 mg it was 0% in five patients...
Omeprazole was defined as having healed if ulcer(s) had attained a mucosal diameter of less than 5 mm and were without pain.
appears to require adequate acid and pepsin secretion, in addition to intrinsic factor secretion, by the stomach. Drugs which inhibit gastric secretion, or have non-specific B12 binding activity (R-factor-like activity), or bind with B12-intrinsic factor complex may thus impair assimilation of food-bound vitamin B12. We have studied the ability of a range of 'mucosal protective' agents to bind with B12 or B12-intrinsic factor complex in vitro, and the effects of a range of 'mucosal protective' agents and gastric antisecretory drugs on the assimilation of egg yolk bound vitamin B12 in patients undergoing treatment for duodenal ulcer disease.

De-Nol, sucralfate, carbenoxolone and antacid-alkaline preparations bound either vitamin B12 or B12-intrinsic factor complex in vitro, but these preparations did not reduce the assimilation of egg yolk bound vitamin B12. Both ranitidine 150 mg and cimetidine 400 mg administered 90 min before the test meal, or ranitidine 300 mg taken on the evening before the test meal significantly reduced the assimilation of egg-yolk bound vitamin B12. Vitamin B12 malabsorption is a possible consequence of longterm therapy with antisecetory drugs, but not with 'mucosal protective' agents.

Effect of bismuth subcitrate on gastric bicarbonate secretion in vitro and in man

C J SHORROCK, J CRAMPTON, L GIBBONS, AND W D W REES (Hope Hospital, Salford) The mode of action of colloidal bismuth in healing peptic ulcers remains unclear. We have examined the action of bismuth subcitrate on gastric bicarbonate secretion; an important component of mucosal defence. Addition of bismuth subcitrate (10⁻⁴ to 10⁻⁴ M) to the luminal side isolated amphibian mucosa, mounted in a Ussing chamber, produced a dose dependant increase in bicarbonate secretion (10⁻⁴ M: 0.19±0.04 to 0.23±0.05; 10⁻⁴ M: 0.17±0.04 to 0.24±0.04; 10⁻⁴ M: 0.28±0.05 to 0.47±0.06 μmol/cm²/h. All means ±SE, n=6 and p<0.05).

Using a previously published perfusion technique the effect of bismuth subcitrate (1-10 mg/ml) on human gastric bicarbonate secretion was studied. Bicarbonate secretion was calculated from the pH4 and pCO₂ of gastric aspirates while acid secretion was suppressed by intravenous ranitidine. After a basal hour, bismuth subcitrate (1-10 mg/ml) was added to the perfusate and bicarbonate secretion measured for another hour at concentrations within the therapeutic range, bismuth did not increase bicarbonate secretion (mean±SE, n=6: 1 mg/ml=593±118 to 611±163; 10 mg/ml=453±114 to 412±86 μmol/h).

These results suggest that stimulation of bicarbonate secretion by bismuth does not occur in man despite being demonstrable in vitro.

ENDOSCOPY

Potential for endoscopic therapy in primary sclerosing cholangitis

S R CAIRNS AND P B COTTON (Department of Gastroenterology, The Middlesex Hospital, London) Over 36 months, 17 of 23 consecutive patients diagnosed PSC received endoscopic therapy. Treatment was sphincterotomy (SPH) alone in five, nasobiliary drainage (NBD) four (two with SPH), intrabiliary steroid infusion (1-BS) five, three with SPH), endoprosthesi (EP) 10 (five with SPH). Balloon dilatations were performed in four patients (three EP, one 1-BS).

Sphincterotomy alone produced a mean fall of bilirubin (Bil) 32%, alkaline phosphatase (ALP) 29%, over 1–11 months (mean six) follow-up. Nasobiliary drainage provided clinical and biochemical improvement in all patients, follow up three to nine months (mean six) with mean fall in Bil 39%, ALP 36%. I-BS was attempted in five patients, successful in four, with mean decrease in Bil 59%, ALP 32%, follow up 1–28 months (mean 16). Endoprosthesi placement succeeded in nine of 10 patients and lowered Bil concentrations (mean decrease 40%) and ALP (mean decrease 27%) in eight patients with substantial symptomatic improvement in six, follow up 1–28 months (mean nine).

Six of nine patients given EP remained well without recurrence of cholangitis with stable LFT’s up to one year after stent extraction.

These results suggest that endoscopic therapy may be useful, at least in the short term, providing biochemical and clinical improvement in most patients with symptomatic PSC.

Randomised comparison of Nd YAG laser (L), heater probe (HP) and no endoscopic therapy (C) for bleeding peptic ulcer

K MATTHEWSON, C P SWAIN, M BLAND, J S KIRKHAM, S G BOWN, AND T C NORTHFIELD (Gastroenterology Units, St James’s and University College Hospitals, London) The Nd YAG laser can significantly reduce rebleeding and mortality rates in bleeding peptic ulcers, but less expensive electrodes systems might be equally effective. This study is a randomised comparison of the best electrode (HP) in our animal experiments) with the best laser (Nd YAG in our clinical trials) and no endoscopic therapy. One hundred and forty three consecutive patients with a bleeding peptic ulcer and a stigmata of recent haemorrhage (SRH) accessible to endoscopic therapy were included. Stratification was according to the type of SRH, and randomisation was biased towards the new therapy (HP). The diagnosis of rebleeding and subsequent management were by a clinician unaware of the therapy given. The rebleeding rate was significantly lower in L (20%) than C (42%) (p<0.05) and HP (28%) was not significantly different from either of the other two groups. There was no significant difference in mortality rate between the three groups (L=2%, C=9%, and HP=10%). Combined analysis of these results with our previous randomised Nd YAG laser trials with identical protocol but only two waves of randomisation showed significantly fewer L than HP rebleeds (14% v 28%, p<0.05) and deaths (2% v 10%, p<0.05). The results confirm Nd YAG laser but not heater probe efficacy, and the combined results show significantly superior results with the Nd YAG laser than with the heater probe.

Multipolar electrocoagulation (MPEC) in the treatment of ulcers with non-bleeding visible vessels (VV): a prospective, controlled trial

L LANE (INTRODUCED BY J VALENZUELA, USC School of Medicine, Los Angeles, CA, USA) This study assesses the efficacy of MPEC in reducing the morbidity of ulcers with visible vessels (VV). Patients with upper GI haemorrhage and (a) blood transfusions of ≥2 units in 12 hours; (b) systolic BP ≥90 mm Hg, heart rate <110 beats/min, or orthostatic changes in systolic BP ≥20 or heart rate ≥20; or (c) haematocrit drop ≥6% in 12 hours were considered for entry (n=466). Patients were randomised to MPEC or sham MPEC if endoscopically showed a VV in an ulcer without active bleeding (n=60). The patient and the physicians were blinded regarding treatment.

The treatment and control groups had no significant differences in any of 29...
characteristics evaluated at the time of randomisation. Results after entry for sham MPEC v MPEC: rebleeding: 12/29 (41%) v 6/31 (19%); blood transfused: 3/0±0.7 v 1.7±0.4 units; emergency surgery: 8/29 (28%) v 3/31 (10%); hospital days: 5.9±7 v 4.3±0.4; and cost: $5270±680 v $3780±480. Although these results appear to favour MPEC therapy, the differences are not statistically significant. One death occurred in the MPEC group (without rebleeding); no patient died in the control group.

This interval report of an ongoing trial is encouraging with regard to the use of MPEC in ulcers with non-bleeding VV. A larger sample size will be required, however, to establish statistical significance in favour of MPEC.

Histology and cytology compared for the diagnosis of neoplastic lesions detected at colonoscopy

J T TAYLOR, A HERBERT, AND G T ROYLE (INTRODUCED BY I TAYLOR) (University Surgical Unit and Department of Pathology, Southampton General Hospital, Southampton) Increasing use of fiberoptic endoscopy in the investigation of the large bowel allows biopsies to be obtained more often than previously. The small size of endoscopic biopsies, however, may be less than ideal for histological diagnosis. We have compared cytology of colonicoscopic biopsy specimens with histological analysis.

Seventy two biopsy specimens were obtained at colonoscopy in 38 patients using a standard 2 mm diameter biopsy forceps. A contact smear was made from the biopsy specimen onto a microscope slide, this being fixed immediately. The same tissue sample was sent for routine histological examination.

One sample submitted for histology and four submitted for cytology were unsuitable for evaluation. The final diagnosis was carcinoma in 15 samples, benign adenoma in 25 and normal mucosa in 32. The sensitivity of cytology for carcinoma was 87%. The sensitivity of histology for malignancy was the same. Both techniques were 100% specific. When results of biopsy and cytology were combined the sensitivity increased to 100%.

Cytology of colonscopic biopsies may be carried out simply and rapidly and is a useful adjunct to conventional histology. The need to repeat biopsies of suspicious lesions is avoided.

Colorectal

Acute septic complications of diverticular disease. A radical approach improves survival

A P. CORDER, J WILLIAMS (INTRODUCED BY PROFESSOR I TAYLOR) (University Surgical Unit, F Level, Centre Block, Southampton General Hospital, Southampton, and Ipswich Hospital, Ipswich, Suffolk) One hundred and two patients with a final diagnosis of complicated diverticular disease undergoing urgent laparotomy because of suspected peritonitis (n=81) or intra-abdominal abscess (n=21) were studied retrospectively. Sixty two patients had peritonitis which was faecal in 16 cases. Forty one per cent of patients had macroscopic colonic perforations, 33% intra-abdominal abscesses and 42% colonic masses. Thirty six patients were treated by excision or exteriorisation of the affected colon, 41 by proximal colostomy and drainage and 25 by drainage or laparotomy alone. Although 21 inpatient deaths were distributed evenly over these three groups, marked differences between the groups in age, antibiotic treatment and severity of pathology made direct comparisons unhelpful. Therefore, using a computer model, the prognostic significance of treatment group was investigated along with 12 other features which included age, medical history, operative findings and antibiotic treatment. A significant advantage in survival to discharge was found for those treated by excision or exteriorisation when other factors were controlled for in this way (p<0.05). In the absence of controlled trials, this is the best evidence of an advantage for a radical approach in the treatment of acute septic complications of diverticular disease.

Is colectomy for severe idiopathic constipation a success?

M A Kamm, P R Hawley, and J E Lennard-Jones (St Mark’s Hospital, City Road, London) The experience of colectomy carried out for severe idiopathic constipation in one hospital over the past 15 years is presented.

Patients with Hirschprung’s disease, megarectum or megacolon, and secondary causes of constipation were excluded. All 44 patients were women and the mean age at operation was 34 years. The mean pre-operative stated bowel frequency was once per 4-7 weeks, and abdominal pain (present in 97%) and bloating were prominent features. Eighty eight per cent used laxatives preoperatively. All patients had a normal barium enema. Colonic transit was prolonged in 33/34 patients. Thirteen of 20 (65%) had inappropriate puborectalis contractions on EMG with straining, and 22/30 (73%) were unable to expel a water filled balloon from the rectum in a test of simulated defecation.

Eleven patients had a caecorectal and 33 patients had an ileorectal anastomosis. Mean follow up was 4-0 years (range two months to nine years). Postoperatively, two-thirds of patients were able to stop using laxatives but 19 patients had diarrhea (>2/day) and this usually persisted. Pain persisted in 70% of patients and remained a major problem. In a third bloating and straining persisted. During follow up five patients developed bowel obstruction and in five constipation recurred. Eleven patients underwent further surgery was performed. Primary anastomosis was achieved in only 47%, however, Laparotomy findings were often at variance with the pre-operative assessment. Wound sepsis developed in 27-6% of cases, post-operative abscess in 15 patients, anastomotic dehiscence in 12.8% and stomal complications in 17.5%. Of the 105 pathological specimens available, pathology in addition to CDD was recorded in 19 cases including inflammatory bowel disease (four), and carcinoma (one). There were 19 deaths in series but only nine were caused primarily by CDD. Faecal peritonitis carried the gravest prognosis (57% mortality rate). The audit has to date identified the necessity for precise definition of the complication and pathology. The need for a larger study has been highlighted in order that recommendations may be made about optimum management for each complication.
because of incapacitating diarrhoea or persistent constipation.

Preoperative physiology studies did not correlate with outcome. Colectomy usually relieves constipation in these patients but pain and other symptoms often persist.

### Faecal diversion in the management of Crohn's disease

M C Winslet, H Andrews, J Alexander-Williams, R N Allan, and M R B Keighley (General Hospital, Birmingham) The role of faecal diversion in the management of Crohn's disease has been reviewed by retrospective analysis of 85 patients who have had 95 defunctioning procedures. Fifty one patients had an elective resection with a stoma to protect an anastomosis (n=38) or for coexistent colitis (n=13). Forty four patients... elective diversion alone as the primary treatment for proctocolitis (n=23) or perianal disease (n=11). Significant sustained remission was obtained in both groups (D=31 (70%) p<0.01, R&D=42 (82%) p<0.001, median follow up 28 (6-24 months). A significant number of patients no longer required steroid therapy post diversion (D=14/16 p<0.01, R&D=21/30, p<0.01). There was a significant improvement in post operative serum indices (D=ESR p<0.05) R&D=Hb p<0.01, albumin and ESR p<0.05. Fifty eight patients have undergone or await restoration of intestinal continuity, proctocolectomy has been carried out in 31 and three have died. Disease relapse occurred in 16 of the 29 patients with continuity restored. Faecal diversion used to facilitate or limit resection, for steroid side effects, to avoid or delay proctocolectomy and for perianal disease. The high rate of remission produced by diversion suggests a faecal factor has a role in the pathogenesis of Crohn's disease.

### Abnormal vagal function in the irritable bowel syndrome

H L Smart and Michael Atkinson (Department of Surgery, University Hospital, Nottingham) Oesophageal symptoms in irritable bowel syndrome (IBS) arise from pathological gastro-oesophageal reflux often associated with oesophagitis. As impaired vagal function has been reported in oesophagitis, we have studied 25 unselected patients with IBS (with and without oesophagitis) to determine whether vagal dysfunction could explain the frequent occurrence of reflux in this disorder. Rising of intra-abdominal pressure normally produces an increase in lower oesophageal sphincter pressure through a vagally mediated mechanism. This response was subnormal in 13 patients. Efferent vagal function, assessed by the ratio of peak acid output after insulin induced hypoglycaemia to maximal acid output after pentagastrin, was subnormal in seven of 23 patients. Cardiac vagal function, assessed by heart rate variability with deep respiration, was abnormal in six of 23 patients. In IBS patients with oesophagitis abnormality of these tests of vagal function occurred with a similar frequency to that previously documented in oesophagitis unassociated with IBS but abnormal vagal function also occurred in patients free from oesophageal disease. Impaired vagal function is common in IBS. This explains the frequent occurrence of reflux in this disorder and may also be important in the pathogenesis of IBS itself.

### Screening for colorectal cancer – an analysis of 132 tumours

G Pye, K C Ballantyne, and J D Hardcastle (Department of Surgery, University Hospital, Nottingham) One hundred and thirty two patients have been diagnosed as having colorectal cancer within the test and control groups of a faecal occult blood screening study for colorectal cancer. In the test group there were 42 screen detected tumours (SDT) and 32 tumours in those who had refused screening. Ten tumours presented symptomatically in patients who had had a negative test. In the control group 48 tumours have been diagnosed.

Twenty four of 42 (57%) of SDT were Dukes' stage A compared with 11/90 (12%) of non-screen detected tumours (NSDT), (χ²=30; p<0.001). One of 42 (2.3%) of SDT were associated with hepatic metastases compared with 23/90 (26%) of NSDT, (χ²=10; p<0.01). Nine of 42 (21%) of SDT were pedunculated polyps treated just by colonoscopic polypectomy compared with 2/90 (2.2%) of NSDT (χ²=14; p<0.001). The mean size of SDT was 31 mm compared with 50 mm for NSDT (χ²=4.2; p<0.001). Eleven of 42 (26%) of SDT were histologically well differentiated compared with 7/90 (10%) of NSDT (χ²=4.9; p<0.05). Three of 42 (7%) of SDT were fixed compared with 22/82 (27%) of NSDT (χ²=6.7; p<0.01).

Although overall benefit from population screening must be judged by longterm mortality, those patients with screen detected tumours have better prognostic factors.
Birmingham Six of the first 92 patients transplanted in Birmingham developed a syndrome of fulminant liver failure with characteristic clinical and pathological features which are presented here. The typical clinical profile was of an initially uneventful postoperative period followed by a sudden, rapid deterioration in graft function resulting in graft failure. All six patients died. The characteristic pathological changes were those of massive haemorrhage and hepatocyte necrosis. Initially these changes were confined to centrilobular areas but later spread to involve entire lobules throughout the liver. Inflammatory changes within necrotic areas were usually mild. The mode of presentation in our six patients resembles other previously reported cases of fulminant liver failure after liver transplantation. The mechanisms underlying this process are poorly understood and a number of aetiological factors including ischaemia, infection and rejection have been proposed. None of our cases had any clinical or pathological features to suggest ischaemia or infection and the changes seen histologically did not resemble other well recognised patterns of rejection. A similar picture of massive haemorrhagic necrosis has recently been described, however, in an animal mode of hyperacute (humoral-mediated) rejection. The possibility that massive haemorrhagic necrosis after liver transplantation represents a form of accelerated humoral rejection is therefore suggested.

Circulating osteocalcin as an index of bone turnover in primary biliary cirrhosis (PBC) pre- and post-liver transplantation

R G P Watson, D Coulton, J A Kanis, P McMasten, and E Elias (Liver Unit, Queen Elizabeth Hospital, Birmingham, Royal Hallamshire Hospital, Sheffield) Osteoporosis is a major complication of chronic cholestatic liver disease. Aetiology is not established and attempts at treatment have been disappointing. Primary biliary cirrhosis patients have reduced bone turnover (Hepatology 1987; 7: 137–42). In a previous report, this was associated with reduced circulating concentrations of osteocalcin (Ann Intern Med 1985; 103: 855–60) a non-collagen bone protein produced principally by osteoblasts. In this study osteocalcin was measured by radioimmunoassay in 32 women with PBC (ages 31–62 years, mean 48) and 52 controls (women aged 35–62 years, mean 48). Osteocalcin levels were lower in PBC’s (mean 8±SD 5.6 ng/ml) compared with controls (16±9±5 ng/ml) (p<0.001). In PBC’s there was no correlation with serum bilirubin, length of history or history of bone fractures. Levels three months to 4½ years after liver transplantation in 10 patients (including eight in whom pre-operative values were available) were increased (45±4±19) compared with pre-transplant PBC’s (p<0.001) and controls (p<0.001).

We have confirmed that circulating osteocalcin concentrations are significantly decreased in PBC. After liver transplantation levels arc supranormal, suggesting that bone turnover is increased. This observation lends support to the hypothesis that hepatic osteodystrophy may be arrested or reversed by liver transplantation.

Liver transplantation for fulminant hepatic failure (FHF)

C Vickers, J Neuberger, J Buckels, P McMasten, and E Elias (Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham) The role of transplantation in FHF is uncertain. The transplant unit has little time to assess patient suitability for the procedure and only a short time period exists during which irreversible neurological complications may supervene. Thus, there is a very short interval to obtain a donor liver. Thirty three consecutive patients (13 M), median age 28 (17–64) developed grade III/IV hepatic coma because of paracetamol overdose (17), viral hepatitis (nine) and other causes (seven). Urgent transplantation was considered in 12 (36%) patients (viral five, other seven). Progressive renal impairment was present in nine. Our criteria for liver replacement was age <55 years, grade 4 hepatic coma for a minimum of 24 hours and deteriorating coagulation. Cases of deliberate paracetamol overdose were excluded. Continuous medical reassessment was made up to the time a donor liver became available, with a median interval of 40 hours (range 10–54).

Of seven patients transplanted five (71%) survived. All of these patients are in good health with median follow up eight months (6–20). Three patients died awaiting a donor liver and two recovered. Of 21 (64%) patients not considered for transplantation 10 (47%) survived, including 54% of paracetamol overdoses.

The results indicate that hepatic replacement may improve survival in selected cases of FHF.

Sulphation and desulphination in normal human liver and primary biliary cirrhosis

SI Qbal, C Vickers, and E Elias (Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham) We have examined the hypothesis that cholestasis in PBC is caused by impairment of sulphation ion transfer. Sulphation of bile salts is important to facilitate their urinary excretion whereas sulphation of sex steroids is important in creating inactive hormone. The activities of lithocholic acid (LC) and estrone (E1) sulphotransferase and sulphatase in normal liver (n=7) and PBC (n=13) were examined. Hepatocyte cytosol was analysed for sulphotransferase activity and homogenate, prepared from the same liver, for sulphatase.

Sulphotransferase was significantly lower in PBC compared with controls for both LC (2-6±3±2±07 v 6±50±3±65, p<0.005) and E1 (0-33±0-29 v 1-23±0-58, p<0.0005) (nmol product formed/mg protein/h, mean±SD). E1-sulphatase activity was not significantly different from normal liver (6-18±2±65 v 4-37±1-84). LC-sulphatase was not detectable in the one normal and one PBC studied.

The results indicate significant depression of LC and E1 sulphotransferase activity in PBC liver. This could cause an accumulation of the hepatotoxic secondary bile acid, lithocholic acid, within PBC liver and impair conversion of free active cholestatic oestrogens to their inactive state.

Natural history of primary sclerosing cholangitis (PSC) HLA antigens as predictors of prognosis

M L Wilkinson, P T Donaldson, B C Portmann, J Karani, and Roger Williams (Gastroenterology Unit, Guy's Campus, UMDS of Guy's and St Thomas' Hosp and Liver Unit, King's College Hosp, London) Survival and natural history of PSC are poorly understood and prognostic variables have not been established. We have previously confirmed a positive association of HLA B8 and DR3 and a negative association of B12 with PSC and suggested a negative association of DR4. To examine natural history, prognostic variables and their relation to HLA antigens the HLA profiles of 54 N. European PSC patients undergoing prolonged follow up study were correlated with clinical, radiological and laboratory profiles and with prognosis. Investigations included yearly liver biopsy and ERCP. Poor prognosis (death or liver
transplantation) was analysed by life tables and correlated with other variables by multivariate analysis. Median survival was over 8½ years. Poor prognosis was not predicted by age, sex, CUC, autoantibodies, piecemeal necrosis, prothrombin time, serum albumin, alkaline phosphatase or immunoglobulin (Ig) concentrations. HLA B8 and DR3 were, however, associated with poor prognosis and there was significant linkage disequilibrium between them compared with 63 laboratory controls. IgM rise (19/45) was associated with HLA A1 B8 and/or DR3. Poor prognosis was also predicted by serum bilirubin, γGT and AST, by histological evidence of cholestasis or cirrhosis and by ERC, particularly extrahepatic appearances.

No specific association between primary biliary cirrhosis and bacteriuria?

A FLOREANI, H MITCHESON, R FREEMAN, M BASSENDINE, AND D JAMES (Departments of Medicine and Microbiology, University of Newcastle Upon Tyne) This study aimed to confirm the reported association between bacteriuria and PBC, and to examine whether this susceptibility is related to liver disease or the ‘dry gland’ syndrome.

(1) Screening study: we examined over six months 403 midstream urine (MSU) samples from 160 consecutive unselected PBC patients (147 F, 13 M), 140 chronic liver disease (CLD) patients (65 F, 75 M), 23 primary Sjögren syndrome (SS) patients (all women). Significant bacteriuria (>10⁵ organisms/ml) was found in 11.2% PBC, 12.1% CLD and 4.3% SS patients (NS). The prevalence of bacteriuria was higher in women (12.2% PBC and 18.4% CLD) than men (9% PBC and 6.6% CLD). Bacteriuria was related to age (p<0.05 in PBC) and was commoner in cirrhotics (PBC Stage I: 5.1%; Stage IV 18.1%, CLD; precirrhotic 4.5% cirrhotic 14.6%). E Coli was the commonest isolate (74% PBC, 63% CLD).

(2) Prospective study: urine specimens were tested monthly (at one, three, and five months by MSU; two, four, and six months by Urictol Dip Slide) from 29 PBC patients – eight ‘early’, 13 ‘intermediate’, eight ‘late’ – six CLD and eight SS (all subjects women). The cumulative rate of bacteriuria of six months was 25% in early, 31% in intermediate, 50% in late PBC and 33% in CLD, 62.5% in SS (NS). The prevalence of bacteriuria was higher by dip slide than MSU (positive dip slides checked by MSU showed 5/16 (31%) false positives) and accounted for the apparent higher prevalence of bacteriuria in SS. Persistent bacteriuria was found in seven PBC, with the same organism in 4/7. No CLD patient showed persistent bacteriuria with the same organism.

This study does not support a unique association between bacteriuria and PBC. Sjögren syndrome does not appear to be an important factor for increased susceptibility to UTI. In both PBC and CLD bacteriuria is more common in elderly women with cirrhosis.

Epidemiology of antimitochondrial antibody seropositivity and primary biliary cirrhosis in the west of Scotland

B M GOUDIE, G MACFARLANE, P BOYLE, A D BURT, C R GILLIS, R N M MACSWEEEN, AND G WATKINSON (Departments of Medicine and Pathology, Western Infirmary, and Cancer Surveillance Unit, Ruchill Hospital, Glasgow, Scotland) During the period 1985–1988 715 patients in the West of Scotland (a region with a population of three million served by a single immunopathology laboratory) were found to be seropositive for antimitochondrial antibody (AMA) using an indirect immunofluorescence technique. Case records have been reviewed in 647 (90%) and liver histology examined in 373 (52%) of these cases. The number of patients satisfying predeterm-ined historical criteria for the diagnosis of primary biliary cirrhosis (PBC) was established for the group in whom liver biopsies were available and the results extrapolated to provide an estimate of the frequency of PBC in the total AMA-positive population. Between 1971–1980 when there was high ascertainment of AMA-positive individuals the incidence of AMA seropositivity was 19 per million per year. The estimated incidence of PBC was 11.4–1.5 per 2 million per year and estimated prevalence 69.5–92.7 per million. There was sub regional varia- tion in the incidence of AMA seropositivity with a predominance of cases in urban/industrial areas. The possibility of space time clustering was investigated using a modification of Knox’s test. No case clustering was shown, the observed number of pairs close in time and space showing good agreement with the expected number assuming no interaction.

Defective measles virus (MV) antigen expression causes persistent MV infection in autoimmune chronic active hepatitis (AICAH)

The British Society of Gastroenterology

D A F ROBERTSON, S I ZHANG, E GUY, AND RALPH WRIGHT (Departments of Medicine and Microbiology, Southampton General Hospital, Southampton) Autoimmune chronic active hepatitis (AICAH) is of unknown cause. High antibodies to syncytial antigens in AICAH suggest a possible role for this virus, which is capable of persistent infection, in incomplete form, in the central nervous system in subacute sclerosing panencephalitis, despite a very high antibody response to some measles virus (MV) antigens. To investigate the possibility that persistent incomplete measles virus infection occurs in AICAH we have measured complement fixation antibodies (CFI) together with Western blot analysis of the antibody response to measles (i.e. antibody positive, biopsy proven), 19 controls with liver disease and 16 other disease controls. Very high antibodies to MV antigens were shown in AICAH (geometric mean CFI 1/512 control 1/32) but these were confined to the nucleocapsid, cellular antigens, and polymerase with absent responses to the glycoprotein, matrix and envelope. These findings, together with the demonstration of sequences from a measles virus nucleocapsid genome in the lymphocytes of 12 of these patients suggests that persistent MV infection may play a role in the pathogenesis of AICAH. The correlation between MV genes encoding viral proteins, and antibodies to the proteins will be described.

Combination chemotherapy in hydatid disease

D TAYLOR, D J MORRIS, AND S RICHARDS (Department of Surgery, University Hospital, Nottingham) Chemotherapy of Echinoccus remains a difficult area. We have previously reported encouraging in vitro animal and clinical results with albendazole and more recently have shown praziquantel to be a very active scolicidal agent in vitro. As these two compounds are completely different (benzimidazole/isquinoline), their ultrastructural effects appear different and they do not share the same toxicity problems, we felt that combination chemotherapy should be considered. Combination chemotherapy has not previously been studied in hydatid disease. Live ovine protoscoleces (E granulosus) were maintained in vitro culture and albendazole (A) 500 µg/l and/or praziquantel (PZ) 50, 20, 10 µg/l was added with suitable untreated controls.
Viability was measured by microscopy/ cosin exclusion at three to four day intervals. Whilst both agents were active alone, combinations reliably achieved better results than either drug alone (A + PZ 50, p<0.02; PZ 50 v PZ 50 + A 500, p<0.05). Subtherapeutic concentrations of praziquantel when given in combination had a significant additional effect on viability (A v A + PZ 10, p<0.05). Combination chemotherapy may allow significant improvements in efficacy and the avoidance of dose dependent toxicity problems.

Liver volume, blood flow and perfusion fall in aging man – an explanation for altered drug metabolism in the elderly

H WYNNE, I H COPE, E MUTCHE, M D RAWLINS, K W WOODHOUSE AND O W JAMES (University of Newcastle Upon Tyne) It has hitherto been assumed that the decreased elimination of oxidised drugs in old age in man was because of age related decreased specific activity of human microsomal mono-oxygenases similar to that found in rodents; but recent studies have shown no decline in the specific activities of several drug metabolising enzymes with age in primates or man. We hypothesised that reduced elimination in man might be because of decreased liver size, liver blood flow, and liver perfusion with advanced age. We examined liver volume by parallel longitudinal beta-scan ultrasounds, using the method of Carr; we calculated liver blood flow from indocyanine Green clearance after iv injection of 0.5 mg/kg. Sixty six healthy volunteers (34 women) age 24–91 years (20 age <40, 23 age 40–65, 23 age 65+) were recruited from hospital staff and local social clubs. None had hepatic, renal, respiratory or cardiac disease assessed by clinical history and examination. All had normal blood count, liver blood tests, none took medications. Correlations between liver volume, blood flow and perfusion with age were assessed by Kendall’s rank correlation.

Liver volume fell from 21.4 ± 0.8 ml/kg body wt age <40 to 19.3 ± 0.7 age 40–65 and 15.5 ± 0.4 age 65+ (p<0.001). Estimated volume was 1470 ml age 24, 945 ml age 91 (linear regression). Liver blood flow fell from 17.6 ml/min/kg body wt age <40 to 15.4 age 40–65, 11.4 age 65+ (p<0.001). Estimated flow was 1260 ml/min/age 24; 655 ml/min age 91 (linear regression). Liver perfusion fell from 0.84 ml/min/ml liver age <40 to 0.81 age 40–65, 0.74 age 65+.

Estimated perfusion was 0.87 ml/min/ml liver age 24, 0–70 age 91. We conclude that the age related decline in liver volume, blood flow and perfusion may be the major component in the liver leading to the fall in clearance of many drugs in aged man.

IgG3 in PBC: raised serum concentrations and increased synthesis by peripheral blood lymphocytes

P BIRD, A FLOREANI, H MITCHESON, O JAMES, AND M BASSINDE (Departments of Medicine and Immunology, University of Newcastle Upon Tyne) Primary biliary cirrhosis (PBC) is an autoimmune disorder characterised by positive antimitochondrial antibodies (AMA) and other immunological abnormalities – notably raised serum IgM. We have previously confirmed that the AMA is predominantly of immunoglobulin subclass IgG3. We have now examined the serum concentrations of IgG3 in 104 PBC patients (diagnosed on conventional biochemical histological and clinical grounds), from two separate areas (70 English and 34 Italian patients – histological Stage I, n=27; II, n=14; III, n=28; IV, n=35). A marked rise in serum IgG3 was observed in both English (mean 615 ± 63% serum standard) and Italian (578 ± 296) patients versus age and sex matched controls (mean 70 ± 22) (p<0.001). Raised IgG3 was similar in patients at all histological stages. There was, however, a significant correlation between serum IgG3 level and AMA titre (r=0.74).

To examine the basis of this raised serum IgG3 (increased synthesis or altered clearance) peripheral blood lymphocytes from 19 PBC patients and 18 age and sex matched controls were cultured in vitro and the immunoglobulin synthesised in the supernatant was measured by capture ELISA specific for total IgG, IgG3 and IgG3 Kappa and Lambda chains. Primary biliary cirrhosis lymphocytes in culture spontaneously synthesised a higher % IgG3 total IgG than controls (p<0.001). This correlated with their serum IgG3 (r=0.69, p<0.001) and indicated that there is increased synthesis of this isotype by lymphocytes in PBC. No evidence for clonally restricted synthesis of IgG3 by PBC lymphocytes was found on analysis of the IgG3 Kappa/Lambda ratio. Some viruses preferentially elicit IgG3 antiviral responses; conceivably identification of factors which trigger this increased synthesis of IgG3 in PBC may provide clues to the underlying pathogenesis of the disease.

Haem arginate therapy for acute hepatic porphyria

K E L MCCOLL, M R MOORE, A HERRICK, M J BRODE, AND A GOLDBERG (University Department of Medicine, Western Infirmary, Glasgow) The acute hepatic porphyrias are caused by hereditary deficiencies of individual enzymes in the pathway of haem biosynthesis. Consequently, there is increased activity of the initial rate controlling enzyme of haem synthesis delta-aminolaevulinic acid (ALA) synthase, over production of the haem precursors formed before the enzyme block and impaired hepatic mono-oxygenate activity related to inadequate hepatic haem synthesis for cytochrome P450 formation. We have studied the effect of a new haem preparation, haem arginate (3 mg/kg/24 h iv for three days) in 20 attacks of acute porphyria in six patients. The mean urinary excretion of the haem precursor ALA pretreatment was 320 μmol/24 h (range 180–602) and this fell to within the normal range (0–40) in each case by the third day of therapy (p<0.001). Leucocyte ALA synthase activity was 1200 nmol ALA/g protein/h (range 530–1800) before therapy and fell to 489 (range 215–720) 24 h after the last infusion. Antipyrene t1/2 (an index of mono-oxygenase activity) was 18.7 h (range 7.2–41) over the 48 h immediately before starting therapy and fell to 8.7 h (range 4.1–12.4) during the first 48 h of treatment (p<0.01).

These results confirm that haem arginate effectively corrects the biochemical manifestations of acute hepatic porphyria and is superior to previously used therapies. The demonstration that impaired hepatic mono-oxygenate activity can be corrected by giving haem arginate indicates that the exogenous haem is being incorporated into functionally active hepatic haemoproteins.

Nutritional support in fulminant hepatic failure: the safety of lipid solutions

ALASTAIR FORBES, CLAIRE WICKS, WILLIAM MARSHALL, PHILIP JOHNSON, PAUL FORSEY, AND ROGER WILLIAMS (King's College Hospital and School of Medicine and Dentistry, Denmark Hill, London) When fulminant hepatic failure (FHF) is prolonged the necessary nutritional support is hampered by concomitant renal failure (limiting possible volumes), by insulin resistance, and by a theoretical need to avoid lipid solutions (risk of toxicity from fat accumulation and by thrombocytopenia). In the present study the
magnitude of the risk of iv lipid administration has been assessed by acute lipid challenge, and by prolonged lipid infusion as part of a parenteral feeding regime. Nine patients with FHF complicated by renal failure and cerebral oedema (from paracetamol intoxication in eight from hepatitis A in one were given 500 ml Intralipid 10% over four hours. The median basal triglyceride level was 0.7 mM (0.4–1.7), that at the end of infusion 12.0 (7.1–22.5), and within eight hours all had levels ≤2.0. There were no complications and platelet counts were unaffected. Four patients with anthropometric evidence of malnutrition went on to receive TPN which included 500 ml Intralipid 20% daily, for 7, 10, 15, and 41 days respectively. No complications attributable to the fat content were observed, liver function tests continued to improve, and serial triglyceride levels did not rise above 1.5 mM. All four patients made a full recovery and it is concluded that lipid solutions may safely be incorporated into nutritional support for patients with FHF.

Carbohydrate meals increase hepatic venous pressure gradient (HVPG) in cirrhotics who have bled from oesophageal varices

P A Mccormack, M Graffeo, R Dick, N Morrall, D Wagstaff, A Madden, N McIntyre, and A K Burroughs (Royal Free Hospital School of Medicine, London)

Protein but not carbohydrate or fat feeding causes a marked rise in hepatic blood flow in normal subjects and protein significantly increases (HVPG) in cirrhotics. We examined the effects of a protein free meal (19 g carbohydrate, 5 g fat and 120 Kcal per 100 ml) on HVPG in 16 cirrhotics (15 men; median age 49 range 20–56; alcoholic n = 10, cryptogenic n = 5, autoimmune n = 1) who had bled from oesophageal varices. Eight received a 600 Kcal (500 ml) and eight a 300 Kcal (250 ml) meal. Pressures were measured before and at intervals of ten minutes for one hour after the meal. Hepatic venous pressure gradient increased in all patients after 600 Kcal rising 29% from 15.6 ±SD 5.1 mm Hg to 20.2 ±SD 6.2 mm Hg at 30 minutes (p <0.01) and by 22% to 19.1 ±SD 6.0 mm Hg at 60 minutes (p <0.01). After 300 Kcal HVPG increased in 7/8 patients, mean HVPG increased from 18.5 ±SD 7.7 mm Hg by 15% to 21.2 ±7.1 mm Hg at 30 min (NS) and by 6% to 19.6 ±8.2 mm Hg at 60 minutes (NS). These results suggest that despite the flow results in normal subjects non-protein meals significantly raise portal venous pressure in cirrhotics with varices and that there is a dose effect which may be of importance in the management of patients following acute variceal haemorrhage and for the longterm administration of portal hypotensive drugs.

Prospective randomised trial of endoscopic sclerotherapy (ES) and transhepatic embolisation (TE) in patients with severe cirrhosis and acute variceal bleeding. Preliminary results

P Bonnire, J F Colombet, A Courtet, M Henry-Amor, C l’Hermine, and J C Paris (Hepato-Gastroenterology and Radiology Departments, University of Lille II, Lille and Biostatistics Department, Villejuif, France) Seventy five Child’s C bleeding cirrhotic patients have been randomised to ES (n = 25), TE (n = 25) or to a control group (C) (n = 25). Initial patient’s characteristics did not differ within the three groups especially for clinical status and bleeding.

The mean time between admission and treatment was 8.3h in ES patients, 8.2h in TE patients, and 6.9 in C patients (NS). (1) A bleeding control was achieved in 25/25 (100%) ES patients, 18/25 (75%) TE patients, and 19/25 (76%) C patients (p =0.02). (2) The mean number of blood units required two days after randomisation was 0.76 in ES patients, 1.8 in TE patients, and 2.4 in C patients (p =0.02). (3) An early rebleeding during hospital stay occurred in 3/24 (12%) ES patients, 1/6 (16%) TE patients, and 5/17 (29%) C patients (NS). (4) Eight patients died (32%) in ES group, 11 patients (44%) in TE group, and 11 patients (44%) in C group during the same period (NS).

We conclude that (1) ES was better than TE and usual medical treatments for stopping active variceal bleeding; moreover, it significantly reduced blood requirements. (2) Although lower in ES, early death rate was not significantly improved by ES or TE as compared with control group.

Is bleeding time a useful test in cirrhotic patients?

D Sprengers, P Grech, P A McCormick, N McIntyre, and A K Burroughs (Royal Free Hospital School of Medicine, London)

Bleeding time (BT), a good test for primary haemostasis, is not routinely done in cirrhotics. Bleeding time and platelet count (PC) correlate directly below 100/101 in hypersplenism thrombocytopenia. Increased bleeding risk is estimated with prothrombin time (PT) ≥17s and/or PC <80x109/1, but no correlation with BT has been made. In 100 cirrhotics PC, PT, partial prothrombin time (PTT), and BT in minutes (simplex II, General Diagnostics) were studied. Forty two had a BT ≥10. Bleeding time correlated with PC, above and below 100/101 (Spearman’s p<0.0001). Of 63 cirrhotics with PC ≥80x109/1, 19 (30%) had a BT ≥10 and 10 (16%) had also a PT <17s. Of 37 with a PC <80x109/1, 17 (38%) had a normal BT and nine (14%) had also a PT ≥17s. Forty five cirrhotics had a PT ≥17s of whom 22 (53%) had a normal BT; 55 had a PT ≤17s of whom 22 (40%) had a BT ≥10. Cirrhotics with BT ≥10, had worse liver function, without correlation between BT and PC, PTT or PC, suggesting that factors other than thrombocytopenia prolong BT.

This is the first report of a statistical correlation between PC and BT in cirrhosis. A PC ≥80x109/1 and/or a PT <17s, however, do not predict a normal BT and vice versa. As plasma fraction products do not correct for abnormal BT and platelets are not usually given for PC ≥80x109/1, an unrecognised abnormal BT may remain uncorrected.

Metallothionein and copper in liver disease with copper retention: a histopathological study

M E Elmes, N J Mahy, J P Clarkson, and B J Asani (Department of Pathology, University of Wales College of Medicine, Heath Park, Cardiff) Histochimical studies of copper and copper associated protein (CAP) correlate poorly with hepatic copper content in Wilson’s disease (WD). By examining immunoreactive metallothionein (MT) immunocytochemically and CuII and CAP using rubenac acid and orcin respectively in 120 diagnostic liver biopsies we attempt to explain this discrepancy and investigate the diagnostic value of MT immunocytochemistry.

In normal liver (n = 25) CuII and CAP were absent and cytoplasmic MT was present in centrilobular hepatocytes. In primary biliary cirrhosis (n = 14) CuII and CAP were often found in paraseptal hepatocytes and MT had a strong overall distribution. Degenerate hepatocytes in piecemeal necrosis were intensely MT positive. In chronic active hepatitis (n = 25) with piecemeal necrosis MT positive cells were prominent against pale MT staining of background hepatocytes in contrast with WD (n = 5) where all hepatocytes were strongly MT positive. In sclerosing cholangitis (n = 4) and nonspecific cirrhosis...
Mitochondrial aspartate aminotransferase (mAST) as a marker for alcohol misuse in patients with liver disease and controls

C G ALVEYN, J BERESFORD, F G BULL, AND RALPH WRIGHT (University of Southampton, Southampton) Eighty three patients (51 men and 32 women) were studied, 22 with alcoholic liver disease, 20 alcoholics with normal liver function tests, 26 with non-alcoholic liver disease, 15 epileptics on anticonvulsants; and 64 normal volunteers (32 M and 32 F) before and after ethanol challenge (1-1 g/kg daily for one week). Alcohol consumption was assessed by questionnaire. Blood samples were taken for routine liver function tests (LFT's), mean red cell volume (MCV), glutamyl transpeptidase (yGT), and mAST by the method of Rej. the ratio of mAST to total AST (tAST) was calculated.

Significant differences were observed in the mAST/tAST ratio, the highest levels in alcoholics currently drinking heavily (median mAST/tAST ratio 21-6%). Those who were drinking moderately (<80 g/day) or had stopped drinking were significantly lower (14-6% and 11-8% respectively). The ratio was significantly lower (median 9-45%) in patients with non-alcoholic liver disease and significantly elevated in epileptic patients on anticonvulsant treatment (median 15-2%). In normal subjects, there was no difference in the mAST/tAST ratio after one week’s alcohol challenge.

When compared with the yGT and MCV the mAST/tAST ratio was a better index of current heavy alcohol consumption than either of these standard parameters.

Glutathione S-transferase levels in autoimmune chronic active hepatitis

F C HAYES, A J HUSSEY, J KEATING, I A D BOUCHER, R WILLIAMS, G J BECKETT, AND J D HAYES (University Departments of Medicine and Clinical Chemistry, Royal Infirmary, Edinburgh and Liver Unit, King's College Hospital, Denmark Hill, London) Serum glutathione S-transferase (GST), a sensitive marker of hepatocellular damage, was measured by radioimmunossay in 26 serum samples from 22 patients with histologically proven, autoimmune chronic active hepatitis (CAH) and compared with aspartate transaminase (AST) levels at various stages of the disease. All but one patient were on steroid therapy and 13 were also receiving azathioprine. In 17 of the 26 paired results, GST was raised compared with only six AST levels. In 11 samples, an abnormal GST was associated with a normal AST concentration. All AST levels in patients with GST levels below 8 ng/l (two times upper limit of normal) were normal and only once when this threshold value of GST was exceeded was there a correlation between GST and AST. Patients with histologically active CAH demonstrated abnormal levels of both enzymes but many patients with chronic persistent hepatitis and little evidence of activity still had normal GST levels.

These data show that ongoing hepatocellular damage is occurring in patients traditionally considered in biochemical remission and may explain why many patients with treated CAH progress to cirrhosis despite treatment.

Effect of high and low protein meals on portal haemodynamics in patients with cirrhosis and portal hypertension

N H AFDHAL, P A MCCORMACK, M KEOGHAN, AND J HEGARTY (Gastroenterology & Liver Unit, St Vincent's Hospital & University College, Dublin) Although splanchic blood flow increases after a meal in normal subjects, the postprandial increases in hepatic blood flow and its relationship to changes in portal pressure in patients with cirrhosis and portal hypertension have not been extensively studied. In this present study the portal pressure (PSG; wedged hepatic venous pressure minus free hepatic venous pressure) and estimated hepatic blood flow (EHBF), calculated using Indocyanine green clearance, was determined in nine patients with cirrhosis and oesophageal varices following a 20 g and 80 g isocaloric, isovolumetric protein meal.

After the 20 g protein meal PSG increased by 22% from 11.6±5.3 mm Hg to 14.2±6.6 mm Hg (Student's t, p<0.01). The 80 g meal PSG increased by 33% from 14.1±5.9 mm Hg to 18.7±5.3 mm Hg (p<0.001). The rise in PSG after the 80 g meal (4.7±5.3 mm Hg) was significantly greater than that occurring after the 20 g meal (2.5±2.2 mm Hg; p<0.05). Maximal increases in PSG occurred at a median time of 20 minutes after the meal and were sustained for a period of observation of up to one hour. The EHBF after the 80 g protein meal increased by 56% from a fastling level of 1399±530 to 2474±530 ml minute. Increases in EHBF occurred within 20 minutes of the meal and coincided with the increases in PSG.

These studies indicate that in patients with portal hypertension protein meals cause significant changes in portal haemodynamics that are dose dependent and related to increases in hepatic blood flow.

Is the reduced vascular tone in cirrhosis caused by ‘desensitisation’ to sympathetic nervous activity?

A J MACGILCHRIST, D J SUMNER, J L REID, AND T J THOMSON (University Department of Materia Medica, Stobhill Hospital, Glasgow) Severe cirrhosis is associated with reduced peripheral vascular tone despite sympathetic overactivity. We have investigated whether sympathetic desensitisation may explain this anomaly. We measured blood pressure (BP) responses to steady state intravenous infusions of the sympathetic agonist noradrenaline (NA) and the non-sympathetic pressor agent angiotensin II (AII) in 10 severe cirrhotics (Pugh’s Grade B or C, group 1), 10 mild to cirrhotics (Pugh’s A, group 2) and 20 healthy controls (group 3), matched for age and alcohol intake. Before the study, the severe cirrhotics had raised plasma NA and lowered BP compared with controls. The dose of NA or AII which raised BP by 20 mmHg (PD50) was calculated from individual dose response curves. Figures are mean±SD, compared by one-way ANOVA after log transformation.

Thus there is reduced vascular responsiveness to both sympathetic and non-sympathetic pressor agents in severe cirrhosis. We conclude that sympathetic desensitisation may indeed occur in these patients, but is not the sole explanation for the loss of vascular tone.

Effect of obstructive and hepatocellular jaundice on triglyceride metabolism

I. ISABEL-MARTINEZ, R J HALL, G R GILES, AND M S LOSOWSKY (University Department of Medicine, University of Cambridge, Cambridge) Obstructive jaundice (OJ) is associated with marked hypertriglyceridaemia, while patients with hepatocellular jaundice (HCJ) have only mild hypertriglyceridaemia. Increased posthepatic triglyceride (TG) turnover in OJ and accelerated TG clearance in HCJ are the main mechanisms of hypertriglyceridaemia in OJ and HCJ, respectively. We examined the distribution of TG in patients with OJ and HCJ and compared these results with those in patients with liver disease but normal serum TG. Internal fat content was determined by 1H nuclear magnetic resonance. The area under the curve (AUC) was calculated as the integral of the TG concentration above the baseline level over time.

In OJ, the AUC for TG was greater than in HCJ and liver disease but normal serum TG; in HCJ, the TG AUC was lower than in OJ and liver disease but normal serum TG. In OJ, the AUC for TG was greater than in HCJ and liver disease but normal serum TG; in HCJ, the TG AUC was lower than in OJ and liver disease but normal serum TG. In OJ, the AUC for TG was greater than in HCJ and liver disease but normal serum TG; in HCJ, the TG AUC was lower than in OJ and liver disease but normal serum TG.
Surgery, St James's University Hospital, Leeds) Jaundiced patients exhibit a number of abnormalities of lipid catabolism. These may have important implications when they require nutritional support. Plasma triglyceride (Tg) turnover was studied in patients with obstructive jaundice (OJ), hepatocellular jaundice (HCJ) and controls with normal liver function. Patients received an intravenous bolus of H₂O₂-glycerol after plasma Tg concentration was confirmed to be in steady state. The decay curve of plasma radiolabelled triglyceride activity was used to obtain the fractional catabolic rate (FCR) and total Tg turnover (V).

Plasma Tg turnover was reduced almost 10-fold in patients with HCJ (19±0.7 mg/kg/h) compared with controls (18-0±2-2 mg/kg/h) or patients with OJ (19-3±3.7 mg/kg/h). The ratios of plasma Tg turnover/concentration suggest that patients with OJ have reduced plasma clearance capacity but normal hepatic Tg secretion. Patients with HCJ have reductions in both hepatic Tg secretion and plasma clearance.

The results indicate that patients with HCJ and OJ may have impaired ability to clear artificial fat emulsions from the plasma. Patients with HCJ may be at risk of developing hepatic steatosis during nutritional supplementations due to their reduced hepatic Tg secretion.

**Interstitial hyperthermia—a new therapy for intrahepatic neoplasms**

AC STEGER, KMATHIUSON, SG BROWN, AND GC CLARK (National Medical Laser Centre, Department of Surgery, University College, London, The Rayne Institute, London) A low power laser coupled to a thin flexible fibre, inserted directly into tissue (interstitial therapy) can deliver energy to the centre of solid organs with great precision and without damage to overlying tissue. This produces local thermal damage which is predictable in nature and extent.

In normal rats we established that the maximum diameter of necrosis produced with a single interstitial fibre was 1-8 cm, with 1 Watt of power for 600s from a Nd:YAG laser. (Below 1 W less necrosis occurred; above 1.5 W severe charring and vapourisation occurred around the fibre tip.) Healing was by regeneration, with minimal scarring within six weeks.

Larger volumes of necrosis were produced in normal canine liver using multiple treatment sites with four fibres activated consecutively or simultaneously from the same laser. Maximum necrosis (7×4 cm) was achieved with 1-5 W for 670 secs down each fibre simultaneously. These lesions healed safely, mainly by regeneration, with little systemic upset.

Larger volumes could be treated using more fibre insertions. Thermally induced necrosis has a potential for treating liver tumours and healing is likely to occur in a similar way to necrosis in normal liver. This possible new treatment for ultrasonically defined intrahepatic neoplasms, should carry a lower morbidity than chemotherapy, partial hepatectomy or liver transplantation.

**Effect of SMS 201-995 on the growth and development of hepatic metastases**

DM NOTI, SA JENKINS, SG GRIME, J YATES, DW DAY, JN BAXTER, AND TG COOKE (University Departments of Surgery, Pathology and Nuclear Medicine, Royal Liverpool Hospital, Liverpool) As reticuloendothelial system (RES) inhibitors promote tumour growth the present study was carried out to establish whether an RES stimulant, SMS 201-995, had any effect on the growth and development of liver metastases. Hepatic metastases were induced in Fisher rats by intraportal injection of 4×10⁷ Walker cells. An experimental group (n=20) received 2 μg SMS 201-995 sc bd commencing on the day of inoculation. Control animals (n=20) were dosed similarly with isotonic saline. All rats were killed three weeks later and the extent of liver replacement by tumour assessed. Hepatic and splenic RES activity was determined by the uptake of ²⁰¹Tc sulphur colloid and the effects of SMS on Walker cell growth measured both in vitro and in vivo. SMS 201-995 significantly inhibited the growth and development of hepatic metastases (p<0.05 Mann Whitney U Test). Thus in two animals there was no tumour and in a further 12 solitary metastases (1-2 cm diameter) were present. In four rats treated with SMS 25% of the liver was replaced by tumour. In contrast in control rats the degree of liver replacement by tumour varied between 60-90%. SMS stimulated the growth of Walker cells in vitro but had no effect in vivo. RES activity was stimulated by SMS, this effect being particularly marked in the liver (liver: blood ³⁰¹Tc-SMS 4-41±0-45, controls 2-20±0-41 p<0.02, Mann-Whitney). These results clearly indicate that SMS 201-995 significantly inhibited the growth and development of experimentally derived hepatic metastases, possibly through RES stimulation.

**Incorporating lipid into soup or main course has different effects on gastric emptying and nutrient absorption**

KM CUNNINGHAM AND NW READ (Sub-Dept of Human Gastrointestinal Physiology and Nutrition, University of Sheffield, Sheffield) Three studies were carried out in each of six volunteers to investigate how lipid, given at different stages during the course of a meal, affects gastric emptying and postprandial blood glucose levels. The meal consisted of 300 ml low nutrient soup, followed 20 minutes later by a 300 g mashed potato. Sixty grams margarine was incorporated into either the soup or the mashed potato. Incorporation of fat into the soup delayed gastric emptying of the mashed potato compared with the fat free control meal (t₁/₂=114±11 v 67±7 min; p<0.05) by increasing the lag phase (31±7 v 2±1 min; p<0.05).
but not affecting the slope (0.9±0.1 v 0.8±0.1%/min). This was associated with a delay (115±13.8 s 57.5±3.3 min; p<0.05) and a reduction of the glucose peak (7.5±0.5 v 9.1±0.5 mmol/l; p<0.05). Incorporating fat into the mashed potato also slowed gastric emptying (t1/2=102±9 v 67±7 min; p<0.05), but by reducing the slope of emptying (0.9±0.1 v 0.6±0.1%/min; p<0.05), not by altering the lag phase (4±1 v 2±1 min). This was associated with a greater reduction, but no delay in the peak glucose level (6.6±0.4 mmol/l) than with the high fat soup. Our results indicate that the effect of fat on gastric emptying and absorption of nutrients depends upon what stage of the meal it is eaten.

Evaluation of the nutritional effects and surgical risks during a two year study after gastroplasty for morbid obesity

D A KELLY, J A ARMISTEAD, AND J A WALKER SMITH (Queen Elizabeth Hospital for Children, London) Sixty eight babies under nine months were studied in order to evaluate the surgical feeding practices. All babies were fed glucose electrolyte mixture (GEM) for 24 hours and then randomly assigned to three groups: group I (n=22) were regraded onto a low solute milk formula (LSM) over four days; group II (n=22) were fed full strength LSM and group III (n=24) were rapidly regraded onto a hypoallergenic whey hydrolysate formula. Babies were followed for five days and reviewed at 14 days. Groups were evenly matched for age, sex, ethnic origin, nutritional state and degree of dehydration. There was no significant difference in vomiting, stool frequency, presence of reducing substances, or duration of hospital stay between the groups. There was poor compliance due to refusal of feeds in the babies fed the whey hydrolysate only (group III). Weight was more rapidly regained in babies in group II although weight gain at 14 days was comparable in all groups. Twelve (17%) babies relapsed (group I=4, group II=5, group III=3). An enteric pathogen was detected in 9/12 and cow’s milk protein intolerance was diagnosed on jejunal biopsy in the remaining 3/12 (one from each group). In this group of previously healthy, well nourished babies with mild acute gastroenteritis there is no advantage in a slow regrade to milk feeds or in feeding a hypoallergenic formula.

Comparative value of tests for small intestinal bacterial overgrowth (SIBO)

D E LOFT, S A RILEY, AND M N MARSH (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) Culture of small intestinal contents is generally regarded as the ‘gold standard’ for diagnosis of SIBO. Many less invasive tests are available but little is known of their comparative value. We have studied, prospectively, the sensitivity and specificity of: (1) jejunal aspirate culture (JC); (2) urinary indicans excretion (UI); (3) glucose hydrogen breath test (GH); and (4) 14C-glucolactone breath test (GC). Thirty four subjects (13 F:21 M) underwent JC, 24 hour UI excretion and simultaneous 50 g GH and GC breath test. Symptomatic response to treatment was assessed following either oral metronidazole or tetracycline. Sixteen of 34 patients had SIBO. Predisposing causes were found in 13.

Human serum IgA response to Giardia lamblia

A K GOLO, D D K ROLSTON, V I MATHAN, AND M J G FARTHING (Dept Gastroenterology, St Bartholomew’s Hosp, and Wellcome Research Unit, CMC Hospital, Vellore, India) Specific serum IgG and IgM responses occur in giardiasis, the latter being helpful in diagnosis. Using ELISA we have now measured specific IgA responses in 78 patients with diarrhoea in the UK and India, 39 of whom had giardiasis. Giardiasis was excluded by multiple stool examinations and in Indian patients by duodenal aspirate microscopy. Anti Giardia IgA titres were higher in control subjects from India (median 100, range 0–200) than in those from UK (0–100). IgA titres for Indian and UK patients with G lamblia were 200 (0–1600) and 50 (0–3200), respectively. Nine of 25 (36%) of UK and four of 14 (28%) of Indian patients with giardiasis had raised IgA titres. Eleven of 39 (28%) of Indian and UK patients with giardiasis had no detectable anti-Giardia IgA; there being no difference in the proportion of IgA-negative patients from each geographic location. Of the five patients on whom convalescence sera were available two to four weeks after parasitic eradication, IgA titres decreased in two, were unchanged in two and rose in one.

Thus specific serum IgA responses occur in giardiasis in approximately one-third of infected individuals. High serum IgA titres (>200) were never found in either Indian or UK disease controls, suggesting that this serological test may be of value in diagnosis when titres are raised, but low titres do not exclude infection.
Intensive dietary counseling in adolescents with cystic fibrosis

J Williams, D A Handy, P H Weller, and I W Booth (Institute of Child Health, University of Birmingham and Birmingham Children's Hospital, Birmingham) Increasing energy intake in patients with CF has been shown to have variable results; failure is frequently associated with poor compliance. Twenty-eight adolescents with CF (9–18; mean: 13.7) were studied over one year to assess the effects of intensive dietary counseling upon nutritional status. They were randomly allocated to three groups: group (A) controls; group (B) received counseling to improve dietary intake to >130% of RDI (expected weight for height) using normal foods and simple supplements; group (C) received counseling and also an enteric coated pancreatic enzyme supplement instead of conventional supplements. The groups were matched for age, sex, and Shwachman score.

Surprisingly, the only group which showed a significant change in weight when compared with the other groups was group B (mean weight SDS change±standard deviation: Gp A, -0.143±0.214; Gp B, ±0.037±0.245; Gp C, -0.131±0.176 (p<0.001)). Although there was also an increase in weight velocity in this group compared with groups A and C, this did not reach statistical significance.

These data suggest that intensive dietary counseling may be more important than enteric coated pancreatic enzyme supplements in improving nutritional status in adolescents with CF.

Effect of ritometan on food pseudo allergy

C André, F André, and L Descos (Laboratoire d’Immunopathologie Digestive INSERM Centre Hospitalier Lyon-Sud, Pierre-Benite, France) Digestive and extra digestive symptoms caused by food pseudo allergy are identical to those of an anaphylactic reaction but are caused by non-specific mechanisms. Gut inflammation may be an important factor in food pseudo allergy. Ritometan (INN) reduced eosinophil chemotactic leucotriene generation and histamine release from mast cells; it reduced PAF synthesis and inhibited C3 activation. Its effectiveness was therefore assessed in seven patients presenting troubles after the consumption of tyramine rich or histamine releasing foods. In these patients prick tests to food were sometimes positive and related to non-specific histamine release but food specific IgE measurements were always negative as well as the detection of jejunal IgE plasma cells.

Gastrointestinal permeability was investigated by the ingestion of 65 ml water containing 5 g lactulose, as a marker of absorption of large molecules and 5 g mannitol as a marker of absorption of small molecules. Complete five hour urine collections were made, volumes recorded and aliquot of each preserved for sugar analysis using gas chromatography.

In 100 healthy subjects mean mannitol excretion was 14.3% (SD±3.3) and mean lactulose excretion was 0.30% (SD±0.20). In the seven food pseudo allergic patients the mean mannitol excretion was 16.0% (SD±5.4) and the mean lactulose excretion was 1.06% (SD±0.55).

Ritometan (1500 mg daily for a week) was associated with clinical improvement. This treatment resulted in a significant increase of mannitol recovery (27.5%; SD±5.6) and in a significant decrease of lactulose recovery (0.62%; SD±0.47).

We concluded that raised gut permeability to large molecules, probably related to inflammation mediators release, may be involved in the pathogenesis of food pseudo allergy. These abnormalities respond to the oral treatment with ritometan.

Immunofluorescent and genetic studies of coeliac relatives of patients with dermatitis herpetiformis (DH): does sub-clinical DH exist?

S O'Mahony and M J Whelton (Department of Gastroenterology, Regional Hospital, Cork, Ireland) Two previous studies found no IgA skin deposits in normal relatives of patients with dermatitis herpetiformis (DH). We have studied a distinct subgroup of relatives of patients with DH, namely those with coeliac disease (CD). We have previously reported on 119 patients with DH, 13 (11.7%) of whom had 21 relatives with a clinical history suggestive of CD. We have established a histological diagnosis in seven of these and have studied skin IgA and HLA typing in this subgroup. All were on gluten free diets. Two had IgA deposits in the skin and one of these had DH. Six were HLA B8 positive, five were HLA A1 positive and all five who had DR studies were DR3 positive. The six probands all had IgA deposits in uninvolved skin and five of the six were B8 positive, four were A1 positive and of three studied two were DR3 positive. The genetic homogeneity and the presence of IgA in the skin in some of the coeliac patients suggests that CD and DH are different manifestations of the same disease process. Patients with CD and IgA deposits in their skin may represent a hitherto unrecognised subclinical form of DH.

A specific small bowel enema appearance in non-responsive coeliac disease

N Mike, U Uodeshi, J Ferrando, and P Asquith (East Birmingham Hospital, Birmingham) In untreated coeliac disease (CD) small bowel enema shows a reduction in the number of jejunal folds, and an increase in the ileal folds, compared with normal. A unique appearance, reversal of the normal jejunoileal fold pattern with atrophy of the jejunum and ‘jejunalisation’ of the ileum is rarely found in longstanding untreated CD.

We have prospectively looked for this reversal pattern. It was not found in 400 patients with various non-coeliac gastrointestinal diseases, nor in eight patients with CD who had a good response to a gluten free diet (GFD). There was a significant reduction in the number of jejunal folds in five untreated CD and 10 non-responsive CD patients, and a significant increase in ileal folds (p<0.02) in non-responsive CD when compared with all other groups, with a reverse pattern in nine of these 10.

The 10 non-responsive CD patients had persisting jejunal villous atrophy despite a strict GFD for over three years, and continuing malabsorption. Five had co-existing hypersensitivity to foods other than gluten, four had coeliac lung disease, two had cutaneous vasculitis, two associated colonic carcinomas and one histiocytic lymphoma. Reversal of the jejunoileal fold pattern specifically identifies those coeliacs with a non-responsive state, who are likely to suffer major complications of CD.

Bread is digested more slowly and incompletely if made from coarse flour

L J O'Donnell, P M Emmett, and K W Heaton (University Department of Medicine, Bristol Royal Infirmary, Bristol) To discover if flour particle size affects starch digestibility we gave 400 kcal breakfasts of wholemeal bread and cheese in random order to ileostomates and normal subjects. Ileostomy starch excretion was measured for eight hours postprandially using amyloglucosidase, also blood glucose and plasma insulin for three hours. With bread made from
Coarsely milled flour, starch excretion (mean ±SD) was 42% greater than with ordinary fine flour (564 ±259 v 397 ±164, p=0.01, n=9). At the same time, plasma glucose and insulin responses were significantly lower. Thus coarse flour when compared to fine flour reduced the area under the concentration curve for both glucose (90±46 v 154±82 mmol/l min, p<0.05, n=9) and insulin (3407±111 v 4138±1249 mmol/l min, p<0.05, n=9). Swing of plasma glucose from peak to nadir was reduced with coarse flour (1.3±0.6 v 1.8±0.6 mmol/l; p<0.01) implying reduced insulin action.

Thus bread made from coarse flour results in slower and less complete digestion so that more starch reaches the colon where it adds to the substrate available for bacterial fermentation. This is consistent with reports of increased faecal weight with coarsely ground cereals. The glucose and insulin data suggest that milling practices designed to produce fine flour may have metabolic implications for the consumer in relation to obesity and diabetes.

**Diarrhoea is related to fat malabsorption and partial villous atrophy in HIV infection in male homosexuals**

A MILLER, P BATMAN, C FARQUHAR, S FORSTER, A PINCHING, W HARRIS, AND G E GRIFFIN (St George’s and St Mary’s Hospital Medical School, London) Jejunal biopsies were taken from 20 HIV antibody positive male homosexuals at different clinical stages of HIV disease (symptomatic six, persistent generalised lymphadenopathy nine, AIDS seven) after a 12 h Trolein breath test (CTBT) to detect fat malabsorption. Each biopsy was microscopically examined for mucosal enteropathogens and villus surface area to volume ratio (SV) was calculated using a Weibel graticule. Patients graded diarrhoeal symptoms as normal, mild (2–4), moderate (4–6) or severe (>6) based on stool frequency. A stool specimen was examined by culture and microscopy to detect enteropathogens.

No enteropathogen was identified in stool or jejunal mucosa. Partial villous atrophy (PVA) was the sole histological abnormality detected in 15 (75%) of biopsies and CTBT correlated with the degree of partial villous atrophy (SV) (p<0.008). The presence of PVA and fat malabsorption were detected at all clinical stages of HIV infection. Ten of 12 patients reporting moderate or severe diarrhoea had evidence of fat malabsorption whereas one of eight patients with normal fat absorption had similar diarrhoeal symptoms (p<0.001).

Thus diarrhoea in HIV antibody positive male homosexuals in the absence of an identifiable enteropathogen is related to jejunal PVA and fat malabsorption. Such diarrhoeal disease can be found at all clinical stages of HIV antibody positive infection.

**Sorbitol malabsorption in normal volunteers and in patients with coeliac disease**

G R CORAZZA, A STROCCHI, R ROSSI, AND G GASBARRINI (I Department of Medical Pathology, S. Orsola University Hospital, University of Bologna, Bologna, Italy) Sorbitol is a hexahydroxy alcohol used as a sugar substitute in many dietetic foods and as a drug vehicle. Previous studies have suggested that sorbitol ingestion may be an additional cause of non specific gastrointestinal distress. We evaluated sorbitol malabsorption in 30 healthy volunteers, seven patients with untreated coeliac disease and nine patients with coeliac disease on a gluten free diet by a four hour H2 breath test. After ingestion of test solution containing 10 and 20 g sorbitol and of four sweets (6–9 g of sorbitol), 98%, 100%, and 62% of healthy volunteers, respectively, showed a significant rise in H2 excretion indicative of sorbitol malabsorption. Out of all healthy subjects tested 100% after 20 g and 50% after four sweets complained of symptoms of carbohydrate intolerance during the eight hour period after sorbitol ingestion. At a 5 g dose given at concentrations of 2%, 4%, 8%, 16% malabsorption was shown in 10%, 12%, 22%, and 43% of the healthy volunteers. Symptoms of intolerance at 5 g were experienced only at concentrations of 8% and 16%. Unlike healthy volunteers and coeliac patients on a gluten free diet, 100% of untreated coeliacs malabsorbed a 2% solution of 5 g sorbitol. Our results show that sorbitol malabsorption and intolerance may result from ingestion of glucose and/or concentrations usually found in many dietetic foods and drugs and underline the need to consider sorbitol malabsorption as a possible and hitherto underestimated cause of gastrointestinal complaints.

**Fasting breath hydrogen (H2) in coeliac disease**

G R CORAZZA, A STROCCHI, AND G GASBARRINI (I Department of Medical Pathology, S. Orsola University Hospital, University of Bologna, Bologna, Italy) We studied the possible clinical significance of the high basal levels of H2 by analysing the breath excreted by the following fasting subjects: 50 healthy volunteers, 149 subjects with functional bowel disorders, 16 patients with small bowel bacterial overgrowth proven by bacteriology. 34 patients with untreated coeliac disease. 40 patients with coeliac disease on a gluten free diet and 40 patients with disorders of the small intestine other than coeliac disease (disease control). The fasting levels of H2 in untreated coeliac patients (22±19 ppm) were significantly higher than those in healthy volun-
Inhibition of starch absorption by dietary fibre

O HAMBERG, J J RUMESSEN, AND E GUDMANN-HOVER (INTRODUCED BY P M CHRISTIANSEN) (Gentofte University Hospital, Dept of Gastroenterology F, Copenhagen, Denmark) Using the H2-breath technic, the effect of three dietary fibres on starch absorption was examined in eight subjects. They received the test meals in randomised order: (a) bread made of 100 g wheat flour, (b) bread made of 100 g low gluten wheat flour, bread (a) with either (c) wheat bran, (d) beet-fibre or (e) pea fibre, and (f) the fibres separately (15 g each). The quantity of H2 excreted in excess of that produced by the fibres alone was calculated.

The percentage of malabsorbed starch were: (a) 8% (4–17), (b) 0% (0–6), (c) 12.5% (5–22), (d) 12.5% (5–20), and (e) 12% (5–27). Low gluten bread was malabsorbed, in small amounts, by only three subjects, p<0.05. The increase of starch reaching the colon when fibre was added was: (c) 80% (+14–133) p<0.05, (d) 36% (11–180) p<0.01 and (e) 66% (33–163) p<0.01. Oroacaeal transit times were: (a) 360 min (210–420), (c) 165 min (120–300) p<0.01, (d) 240 min (90–360) p<0.05 and (e) 270 min (90–300) p<0.05.

We conclude that the dietary fibres impaired starch absorption, and this may be an important factor in the regulatory effects of dietary fibres on bowel function. The gluten moiety seems to possess inhibitory qualities to starch absorption. All three fibres decreased oroacaeal transit time.

Effects of vitamin E deficiency on small intestinal transport function

M SATO, M GOSS-SAMPSON, D P R MULLER, AND P J MILLA (Institute of Child Health, London) The gastrointestinal mucosa is vulnerable to damage by lipid peroxidation. Vitamin E (E) is a powerful membrane bound anti- oxidant present in high concentration in enterocytes. We have studied the effects of E deficiency on mucosal function. Twenty days old male Wistar rats were placed on a diet either deficient in E or one to which E (100 mg/kg) had been added. Brush border membrane vesicles of small intestine were prepared by a Ca++ precipitation method and glucose and sodium uptake measured. Na-K-ATPase, cAMP and cGMP were determined in mucosal homogenates. Na+ stimulated glucose uptake was rapid with an ‘overshoot’ in both groups but after nine months of E deficiency maximal glucose uptake was significantly impaired (757±116 v 1152±324 pmol/h/mg protein; mean±1 SD; n=5; p<0.05). H+ stimulated Na uptake was similarly reduced (380±148 v 743±181, p<0.04). In the absence of a Na+ or H+ gradient uptake of glucose and Na+ was not affected by E deficiency. No significant differences in the Na+-K+-ATPase activity or cyclic nucleotide concentrations were observed. These data show that intestinal transport is disturbed in E deficiency and suggest that this is because of an effect on apical membrane transporters rather than on passive permeability or the enterocyte Na+ pump. We speculate that E deficiency may contribute to the malabsorption seen in some states of malnutrition.

Skeletal myopathy secondary to selenium deficiency

D A KELLY, A SHENKIN, A COE, AND J A WALKER-SMITH (Queen Elizabeth Hospital for Children, London, and Glasgow Royal Infirmary, Glasgow) A two year old girl with microvillous atrophy was maintained on longterm home parenteral nutrition (HPN). She presented with severe myalgia and regression of walking skills. Investigations: normal full blood count, electrolytes, liver function tests and transaminases. Serum concentrations of vitamins A, E, and B12, folate, zinc and copper were normal. Plasma selenium was very low at <0.05 mol/l (reference range (RR) 0.8–2.0 mol/l); RBC glutathione peroxidase was undetectable at 1/100 Hb and plasma glutathione peroxidase was 6/1 (RR 90-35l. RBC enzymes showed normal B1, B2, B4 status. Electromyogram was mildly abnormal. Muscle biopsy showed atrophy of type II fibres and muscle selenium was 0.23 g/kg dry weight (adult RR: 0.6–0.97 g/kg). Chest radiograph, ECG and echocardiogram were normal. Fifteen grams per day sodium selenite was added to HPN and no other change was made. Within three days muscle pain had improved; she began to crawl again and by six weeks she was walking normally. At three months, plasma selenium had risen to 0.53 mmol/l and RBC glutathione peroxidase was 15 μg/l. Although biochemical selenium depletion occurs in adults and children on long term HPN, symptomatic dependency is rare and poorly understood. The dramatic response to selenium repletion alone suggested that it caused the myopathy. Selenium is widely available in food but children with severe malabsorption on HPN are particularly at risk from selenium deficiency and parenteral supplementation should be routinely considered for these patients.

Intestinal pseudo-obstruction: is manometry helpful?

D KUMAR, D L WINGATE, N S WILLIAMS, AND H A THOMPSON (Surgical and Gastrointestinal Science Research Units, The London Hospital Medical College, London) The diagnosis of a primary disorder of small bowel motility is difficult and frequently missed on clinical and radiological examination. Manometric evaluation may help confirm the diagnosis and indicate a specific motor abnormality so that management may be rationalised. We have carried out small bowel manometry in 14 patients (age 19–60 years) with a suspected primary disorder of gut motility and 30 control subjects (age 18–55 years). Small bowel manometry was done using an eight port perfused tube assembly and a low compliance Arndorfer pump. Manometric evaluation confirmed the diagnosis in 12 of 14 patients (85%), and thus eliminated a psychiatric disturbance. Motor abnormalities included bursts of contractions occurring every 20–30 minutes in five patients, abolition of motor complexes in one, tachygastria (5–6/min) in one (normal 3/min), fast duodenal contractions (16–18/min) in two patients (normal 9–11/min), retrograde peristalsis in one and absence of motor quiescence following a Phase III front in three patients. None of the control subjects showed any of these abnormalities. In the other two patients based on normal manometry, it was possible to exclude a primary motility disorder.
Intestinal manometry is thus an essential investigation for the diagnosis and management of patients with suspected primary gut motility disorders.

Ontogeny of small intestinal motor activity

W M Bisset, J B Watt, R P A Rivers, and P J Milla (Department of Child Health, Institute of Child Health, WC1, St Mary’s Hospital Medical School, London) In the preterm infant the characteristic patterns of small intestinal motor activity are poorly developed. Using continuously perfused multilumen nasojejunal catheters we have studied the development of such motor activity in 12 preterm infants (28–42 weeks gestation). Fasting activity was studied longitudinally on 28 occasions and on 23 occasions the motor response to enteral feeds was measured. With increasing gestational age a clearly defined maturation of fasting motor activity was seen with increases in: average duodenal pressure 2–12 mm Hg (p<0.001); slow wave frequency 10.5–12.5 cpm (p<0.005); propagation index 1–5 (p<0.001) and a progression from random activity at 28 weeks, through repetitive fetal complexes to migrating motor complexes by 37 weeks gestation. Nutritive sucking only occurred after 33 weeks gestation. Bolus feeds appropriate to the infants age produced no motor response in the very preterm infants (28–30 weeks) but with increasing gestational age (p<0.005), volume of feed (p<0.001) and time exposed to feed (p<0.001), the length of postprandial activity increased (0–140 min). Disruption of fasting activity, however, did not occur when low volume continuous feeds were used. These data suggest that the development of fasting motor activity and nutritive sucking is gestationally dependent whereas the postprandial motor response is dependent on the pattern of feeding. We speculate that the former mirrors central and enteric neural development whilst the latter is more likely humoral related.

Effect of ileal infusion of fats, detergents and bile acids on stomach to caecum transit time in the rat

Nicola J Brown, A Richardson, R D E Rumsey, and N W Read (Sub-Department of Human Gastrointestinal Physiology and Nutrition, The University, Sheffield) We have recently shown that ileal infusion intralipid (a triglyceride) significantly increases stomach to caecum transit time (SCTT). This study aimed to investigate the nature of substances exerting this delayed transit. Twenty two rats (250–300 g) with ileal cannulae (20 cm proximal to the ileocecal valve) and six rats with isolated ileal Thiry-Vella loops (7 cm) cannulated for external infusion were used. After an 18 hr starvation, test substances were infused into the ileum for 20 minutes (0–3 ml/hr) before the rats were fed 5 ml beans by gavage. The infusion continued for a further 160 min. Excreted hydrogen was monitored continuously to give an index of SCTT. Delayed SCTT of the bean meal was observed during infusion of a triglyceride (corn oil, p<0.02), a free fatty acid (oleic acid p<0.02), detergents (AOT, SLES p<0.02), a bile acid (deoxycholate p<0.05), a polysaturated oil (borage, p<0.05) and the fat analogue sucrose polyester (p<0.05) when compared with control infusions. Triglyceride infusion (intralipid) directly into isolated ileal loops also delayed SCTT (p<0.01), suggesting that breakdown of triglycerides to fatty acids is not essential for ileal inhibition of gastrointestinal transit.

In summary we have shown that a range of lipid substances, detergents and bile acids when infused either directly into the intact ileum or into an isolated ileal loop delay SCTT of a bean meal.

HLA D/DR Ag expression in the jejunum of children with idiopathic protracted diarrhoea (IPD) and circulating enterocyte antibodies (EcAb)

R Mirakian, C A Richardson, J A Walker-Smith, S Hill, P J Milla, and G F Botazzo (Middlesex, Queen Elizabeth Hospital, and Hospital For Sick Children, London) Small intestinal villous enterocytes express Class II molecules whereas crypt cells do not. The role of such molecules in the gut is unknown but it has been suggested that they may be involved in maintaining tolerance to oral antigens. In some children with IPD, circulating EcAbs are present together with other autoimmune manifestations. Jejunal biopsies from nine children with IPD, EcAbs and an enteropathy were compared with histologically normal jejunum from nine controls. We studied HLA Class I and II molecule expression in the enterocyte epithelium by immunofluorescence. HLA Class I products were normally expressed in the jejunal epithelium of IPD patients. Class II (DR complex) expression in controls was restricted to upper villous enterocytes. In six of nine patients with IPD and EcAbs (titres >1:64) aberrant expression of DR molecules was seen in crypt enterocytes. It can be suggested that by analogy with a similar phenomenon detected in glands from patients with classical autoimmune diseases, DR+ve crypt enterocytes would be able to act as Ag presenting cells, bypassing macrophage requirement. In the other three patients with EcAbs (titres <1:8) a decreased reactivity was seen in villous enterocytes. In all nine patients numerous DR+ve cells were present in the lamina propria compared to controls. We postulate that aberrant MCH molecule expression in the small intestine might reflect loss of tolerance to luminal antigen which could lead to autoimmune disease.

Portal and peripheral blood short chain fatty acid (SCFA) concentrations after caecal lactulose installation at surgery

E W Pomare, S Peters, and A Fisher (Department of Medicine, Wellington School of Medicine, Wellington, New Zealand) The fate of the major SCFAs (acetate, propionate, butyrate), in man which result mainly from the fermentation of carbohydrates is largely unknown. We have studied fermentation in vivo by measuring these SCFAs in portal and peripheral blood, after the caecal administration of lactulose to patients maintained on polysaccharide free food before undergoing elective cholecystectomy. At operation portal and peripheral venous blood samples were taken before, and at 15 minute intervals up to 60 minutes following, caecal injection of either 20 ml sterile saline (n=12), or 6–7 g (n=6) or 10 g (n=10) lactulose – samples were analysed by GLC. Fasting levels (n=28) were (μmol/l, mean±SD); portal acetate 128±70.8, propionate 34±23.3, butyrate 17.6±18.5; peripheral acetate 77.2±56.1, propionate 3.7±1.2, butyrate traces only. After lactulose there was a rapid rise in portal SCFA, with mean peak levels (μmol/l) after 10 g lactulose being acetate 197, propionate 27.7, and butyrate 17±3 – the response was dose related. No appreciable changes in peripheral SCFA were found. In conclusion, the caecal fermentation of lactulose is rapid in man with appreciable increases in portal SCFAs.

Gastrointestinal bleeding from other sources in patients with colonic angiodysplasia

A C Steger, R B Galland, A Hemingway, C B Wood, and J Spencer (Depts of Surgery and...
School, A 1
Sheffield) chloride sweat cystic scopy cause permeability. Although identify of a using 5% In PAFDIA
Physiology, results from (CF) actively bleeding. Jejunal diverticulum and GI bowel lesion patients having right hemicolectomy and right surgery came to full uncertain, is essential. If at removed came to the small intestine same J of HIARDCASTLE, of Edinburgh had published presentation of those with Crohn’s disease in Scottish children ROGER BARTON, SANDRA GILSON, AND ANNE FERGUSON (University of Edinburgh and Western General Hospital, Crewe Road, Edinburgh) From Scottish hospital inpatient records from 1968–1983, 282 children were identified with the onset of Crohn’s disease (CD) at or before age 16. The incidence has increased four fold from 6-6/million age ≤16 in 1968 to 26-4/million in 1983. This increase occurred within the ages of 9–16, CD remaining rare under the age of nine. A representative sample of 68 cases was investigated in detail. The mean age at onset was 12-6 years, with a follow up of 7-05 (SD±4-2). Each child spent 81-5 days (range 7–322) in hospital, with a mean of 4-4 admissions up to the age of 20 years alone. Disease distribution and presenting features were similar to published large adult series. Forty patients (72%) have already required surgery, 14-5% (10) have a permanent stoma. During the period of the study there were five deaths, a mortality rate of 7%. This unbiased, unselected cohort of Crohn’s patients show no unusual features of the disease itself when presenting in childhood (although of course there are significant effects on growth and nutrition), however, a substantial social and clinical morbidity and mortality is seen. Cystic Fibrosis Unit, Queen Elizabeth Hospital for Children, London) Lactose intolerance has been described in children presenting with cystic fibrosis, but little if any has been written about cow’s milk protein intolerance in this disease. Children with cystic fibrosis commonly present with failure to thrive. Causes include poor dietary intake, recurrent chest infections, and pancreatic enzyme insufficiency. If children attending a paediatric cystic fibrosis clinic continued to gain weight at less than the normal velocity, even after adequate treatment for the above problems, small bowel biopsy was performed (seven cases). In five (aged less than one year) a patchy enteropathy compatible with a histological diagnosis of cow’s milk sensitive enteropathy, was seen. In all cases removal of cow’s milk (and lactose) from the diet resulted in improved weight gain, and stool consistency. Three underwent repeat small bowel biopsy which was normal. Four tolerated cow’s milk by three years: the fifth remains on the exclusion diet at a year old. On review of the clinical features, all had had cystic fibrosis diagnosed within a few weeks of birth. Three of the five had presented with meconium ileus (overall only 10% do so).

Cow’s milk elimination has a significant impact on failure to thrive in some patients with cystic fibrosis (1:30 attending our clinic). Presentation with meconium ileus appears to be common in this group. Small bowel biopsy is an essential investigation in those with cystic fibrosis with poor growth in spite of adequate treatment.

Absence of secretory response in jejunal biopsies from children with cystic fibrosis C J TAYLOR, P S BAXTER, J HARDCASTLE, AND P T HARDCASTLE (Depts of Paediatrics and Physiology, University of Sheffield, Sheffield) The demonstration of reduced chloride absorption and secretion across sweat duct and respiratory epithelia in cystic fibrosis (CF) suggests that the disease results from a specific defect in chloride permeability. Although GIT manifestations of the disease are common and secretory processes in the normal intestine extensively studied no attempts have been made to identify a possible intestinal chloride transport defect in CF.

To address this problem the secretory activity of jejunal biopsies from children with cystic fibrosis has been investigated using a modified Ussing chamber technique. Samples from three children with cystic fibrosis failed to respond when challenged with the intestinal secretagogues acetylcholine and prostaglandin E2, while control tissues exhibited a rise in potential difference and short circuit current in response to these agents. Both groups of tissues generated an increased potential difference and short circuit current associated with sodium linked glucose absorption. These results demonstrate for the first time that the defect in chloride transport observed in other epithelia in cystic fibrosis also exists in the jejunum and could contribute to the intestinal effects of the disease. The technique used should permit further studies of the basic defect and may be of diagnostic value.

Incidence, morbidity and mortality of Crohn’s disease in Scottish children ROGER BARTON, SANDRA GILSON, AND ANNE FERGUSON (University of Edinburgh and Western General Hospital, Crewe Road, Edinburgh) From Scottish hospital inpatient records from 1968–1983, 282 children were identified with the onset of Crohn’s disease (CD) at or before age 16. The incidence has increased four fold from 6-6/million age ≤16 in 1968 to 26-4/million in 1983. This increase occurred within the ages of 9–16, CD remaining rare under the age of nine. A representative sample of 68 cases was investigated in detail. The mean age at onset was 12-6 years, with a follow up of 7-05 (SD±4-2). Each child spent 81-5 days (range 7–322) in hospital, with a mean of 4-4 admissions up to the age of 20 years alone. Disease distribution and presenting features were similar to published large adult series. Forty patients (72%) have already required surgery, 14-5% (10) have a permanent stoma. During the period of the study there were five deaths, a mortality rate of 7%.

This unbiased, unselected cohort of Crohn’s patients show no unusual features of the disease itself when presenting in childhood (although of course there are significant effects on growth and nutrition), however, a substantial social and clinical morbidity and mortality is seen.

Simplified and accurate oral pancreatic function test for use in children J W L PUNTIS, J D BERG, D SULE, AND J W BOOTH (Institute of Child Health, University of Birmingham, Birmingham) The use of 14-C labelled PABA in conjunction with the BT-PABA (Bentiromide) screening test for pancreatic insufficiency (PI) is unacceptable in children. We substituted p-amino salicylic acid (PAS), a structural and pharmacokinetic analogue of PABA, for 14-C PABA. This modified test was evaluated in 28 children with PI (25 cystic fibrosis, two Shwachman’s syndrome, one pancreatectomy), aged 17 months–16 years, together with a group of 20 control patients aged 4 months–11 years, shown to have normal pancreatic function by pancreozymin secretin testing. After an overnight fast, BT-PABA (15 mg/kg) with 4.5 mg/kg PAS was administered with a stand-
ard breakfast of cereal and milk. Following this, a six hour urine collection was made. After the alkaline hydrolysis of PABA and PAS conjugates, urine samples were assayed by HPLC. The PABA Excretion Index (PEI) was derived from the ratio of PABA/PAS urine concentrations. The mean PEI in patients with PI was 19 (range 4–60) and for controls, 87 (range 66–140), with complete separation between patients with PI and those without. We conclude that the exocrine pancreatic status of children may be quickly and accurately determined by a six hour oral test incorporating BT-PABA and PAS.

Pathophysiology of childhood duodenal ulcer

P K H TAM (INTRODUCED BY PROFESSOR R SHIELDS) (DEPARTMENT OF CHILD HEALTH, ROYAL LIVERPOOL CHILDREN’S HOSPITAL, ALDER HEY, EATON ROAD, LIVERPOOL) Very little pathophysiological data on childhood duodenal ulcer exist. Is the childhood condition similar to or different from the common adult disease? We studied gastric acid secretion, emptying rate and serum gastrin concentrations in a group of children with primary chronic duodenal ulcer and a group of normal children as control.

Both BAO and MAO were significantly higher in DU (n = 30) (mean ± SD = 0.16±0.12 mmol/kg/h, 0.55±0.16 mmol/kg/h respectively) than in normal (n = 33) (0.09±0.06 mmol/kg/h, 0.30±0.11 mmol/kg/h) (p < 0.01). In addition patients with more severe disease (n = 15) had higher MAO (0.63±0.17 mmol/kg/h) than those with mild disease (n = 15) (0.47±0.17 mmol/kg/h) (p = 0.02).

Gastric emptying rates were similar in DU (median = 6.8 min) and normal (7.0 min). (p > 0.01). Fasting serum gastrin concentrations were significantly higher in DU (n = 25) (60±4±9.7 pg/ml) than in normal (n = 25) (38±2±4.2 pg/ml) (p < 0.05). Integrated gastrin response to meal stimulation was also significantly higher in DU (14±2±2 ng/min/ml) than in normal (6±4±9 ng/min/ml) (p < 0.001). There was no significant correlation between acid secretion and gastrin levels.

Of the 25 DU patients, 11 had hypergastrinaemia (mean±2 SD) alone, six had acid hypersecretion alone, two had both hypergastrinaemia and acid hypersecretion and only six had both normal gastrin and acid levels.

Our study suggests that there are both similarities and differences between childhood DU and adult DU. Unlike adults, paediatric patients not only have excessive acid and gastrin response to stimulation, they also have increased basal acid and gastrin secretion. The prognostic value of acid study in childhood DU is unique. Findings of gastrin study in childhood DU, never reported previously, suggest that this gastrointestinal hormone is implicated in the pathogenesis of the disease in more than half of the patient population.

Campylobacter associated gastritis in children

M J MAHONY, J WYATT, AND J M LITTLEHEIR (INTRODUCED BY J KELLEHER) (DEPARTMENTS OF PAEDIATRICS AND PATHOLOGY, ST JAMES’S UNIVERSITY HOSPITAL, LEEDS) Gastric colonisation by Campylobacter pyloridis is strongly associated with non-auto immune gastritis in adults, where its significance remains controversial. Its importance in children is unknown. Since 1981, 38 children presenting with persistent epigastric pain (aged 1–16, mean 10±3 years, 21 boys) have undergone upper gastrointestinal endoscopy with gastric biopsy at this hospital. These biopsies were studied retrospectively for C pyloridis colonisation using the modified Giemsa technique, and for the presence of inflammation (Whithead’s classification). C pyloridis colonisation was detected histologically in 9/38 (24%) cases, six of whom were boys. All patients were aged 10 or over, 9/28 (32%) being positive in this group. Eight of the ten patients with chronic gastritis were C pyloridis positive; one of six cases showing only small focal accumulation of lymphocytes was positive, while all 21 with normal gastric histology were negative. We detected C pyloridis in 32% children aged 10 or over endoscoped for epigastric pain. The association between C pyloridis and chronic gastritis in children, in whom gastritis is generally uncommon, supports a causal relation between the bacteria, gastric inflammation and epigastric symptoms.

Pepitic ulcer in childhood: the long term prognosis

M S MURPHY AND E J EASTHAM (DEPARTMENT OF CHILD HEALTH, ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE) Information is limited concerning the long term prognosis for paediatric peptic ulcer disease. We have followed up 19 individuals in whom this diagnosis had been made 14 to 27 years earlier, based on strict diagnostic criteria. The subjects had ranged in age from 7 to 14 (median 12) years at diagnosis and from 25 to 38 (median 30) years at follow up. Nine (47%) had had a proven ulcer on investigation, since entering adult life. Ten (53%) were no longer prone to recurring episodes of abdominal pain but four of these had undergone vagotomy and pyloroplasty for intractable symptoms in the past. Thus, only six patients (31%) appeared to have made a lasting and spontaneous recovery. Complications such as haemorrhage, penetrating duodenal ulcer, severe pyloric stenosis or perforation had occurred in 10 (53%). Seven (37%) had undergone surgery, and in two of these cases more than one operation had been performed. Fifty eight per cent of all complications suffered and 89% of all surgical operations performed were in patients over the age of 21 years. Our findings firmly reinforce the view that paediatric peptic ulcer disease frequently persists into adult life and a risk of potentially life threatening complications remains many years after diagnosis.

Gastro-oesophageal reflux in the preterm infant

S J NEWELL, J W Boot, M E MORGAN, AND A S MCNEISH (REGIONAL NEONATAL INTENSIVE CARE UNIT, BIRMINGHAM MATERNITY HOSPITAL, AND INSTITUTE OF CHILD HEALTH, UNIVERSITY OF BIRMINGHAM, BIRMINGHAM) The incidence, severity and importance of gastro-oesophageal reflux (GOR) in the pre-term infant is unknown. Twenty four hour intragastrical pH monitoring was performed using a novel 1 mm antimony pH electrode (Synectics Medical) and lower oesophageal sphincter pressure measured.

Fifty six measurements were made on 34 patients (postconceptional age: median 31, range 26–29 weeks). Mean (±SEM) indices of GOR were as follows: 12±1±2 episodes of GOR per 24 h; pH was < 4 for 4.5±±±0.9% of the total time; the longest episode during each recording was 17±±±0.6 min. There was no correlation between GOR and postconceptional age, gestation, or lower oesophageal sphincter pressure.

The effect of nursing care upon GOR was assessed. Gastro-oesophageal reflux was most likely to occur at the time of physiotherapy, oropharyngeal suction, and nappy change (p < 0.001), and was increased after feeds (0.05 < p < 0.1). Reflux was slightly increased in the left lateral position. Infants receiving xanthine for apnoea had a two fold increase in GOR (p < 0.05). A group of
six infants with recurrent apnoea had markedly severe GOR (p<0.001). A rapid reduction in the frequency of apnoea followed abolition of GOR with thickened feeds.

These results provide important physiological data and have implications in the nutritional care of the very low birth weight baby.

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**OESOPHAGUS**

**Factors influencing survival in oesophageal cancer**

A Watson (Royal Lancaster Infirmary, Lancaster) Survival after resection for oesophageal cancer is poor, five year survival rate (5YSR) seldom exceeding 15% in the West, although 5YSR greater than 50% for superficial lesions is reported from Japan. It is unclear whether this relates to earlier detection or a different form of the disease. This study was undertaken to investigate the relationship between tumour staging and survival in 49 patients undergoing resection between 1975–81 previously presented to this Society. Forty three of these have now been followed for at least five years and stratified according to cell type, depth of tumour invasion and contiguous lymph node status.

Five year survival rate in resected patients was 14-3% overall and 16-3% in those surviving resection, representing 29-4% for squamous and 7-7% for adenocarcinoma. Nodal involvement occurred in 58-8% of squamous and 80-7% of adenocarcinoma, where 5YSR was 10% and 0% respectively. In node negative cases, 5YSR was 57-1% for squamous and 40% for adenocarcinoma. 23-6% of squamous and no adenocarcinomas were confined to the oesophageal wall. 5YSR in this group being 75%.

Depth of invasion and nodal status are better prognostic discriminants than cell type. Survival in the minority of lesions detected early is comparable to that of Japanese series and to equivalent stages of other tumours.

**Laser therapy or intubation for palliation of malignant dysphagia**

H Barr, N Krassner, A Raouf, and R J Walker (Gastrointestinal Unit, Walton Hospital, Liverpool) A prospective randomised trial was done to compare laser therapy with endoscopic intubation for inoperable oesophageal carcinoma. It was not possible to directly randomise into laser versus intubation, as most patients were not suitable for immediate intubation (because of complete obstruction or tortuous tumour). Patients were randomised into laser followed by repeat laser endoscopy every four weeks (L), or initial laser therapy to ensure a suitable lumen to allow dilatation and intubation (I). Forty five consecutive patients were treated (20L, 20I and five exclusions). Swallowing ability was recorded on a 0–4 scale (0=swallowing all solids, four=total dysphagia). Quality of life was assessed by the QL index (scale 0-10 and a linear analogue self assessment (LASA, scale 0–200). Mean swallowing grade pretreatment was 2.9±0.8(L) and 2.8±0.4(I) (NS). The best post treatment was 0.9±0.2(L) and 1.6±0.5(I) (p<0.002). The QL and LASA improved by 0.7 and 13-1(I) and by one and 20-1(L). Seven (I) and three (L) developed recurrent dysphagia with seven (I) and two (L) having complications. Laser therapy offers more effective palliation for malignant dysphagia than intubation.

**Manometric interpretation of the oesophageal egg transit test: a useful screening test for oesophageal motility disorders**

C A Erikson, R J Holdsworth, D Sutton, N Kennedy, and A Cuschieri (Departments of Surgery and Nuclear Medicine, Ninewells Hospital & Medical School, Dundee) The use of manometry to detect oesophageal motility disorders requires expertise in its performance and interpretation. The oesophageal egg transit test (OET) uses a standardised 99mTc solid egg bolus to objectively and physiologically evaluate oesophageal transit. We assessed the oesophageal motility of 102 symptomatic patients using oesophageal manometry and OET. Of 32 patients with normal OET, 10 (31%) had abnormal manometry (7/10 being diagnosed non-specific oesophageal motility disorder). Of 70 patients with abnormal OET, 51 (73%) had abnormal manometry (5/15-82, p<0.001). The computer generated condensed image defined five different transit patterns: normal (n=32); oscillatory (n=21); non-clearance (n=16); 'step' delay (n=16); miscellaneous delay (n=17). Normal OET correlated significantly with normal manometric parameters. Oscillatory OET showed significantly more tertiary contractions, low amplitude waves and non-propagating swallows, and confirmed the manometric diagnosis of achalasia (6/6) and diffuse oesophageal spasm (2/4). The remaining three patterns of abnormal OET did not significantly correlate with specific manometric parameters or symptom score. The solid bolus oesophageal transit test provides an objective screening test of oesophageal motility disorders and should be performed before oesophageal manometry.

**H2 antagonists in oesophagitis: can physiological studies predict the response?**

D A F Robertson, M A Aldersley, H J Shepherd, R S Lloyd, and C I Smith (Department of Medicine II, Southampton General Hospital, Southampton) The response to H2 antagonists in reflux oesophagitis is disappointing with only 50% of patients healing. In an attempt to identify factors predicting response we have measured: ambulatory oesophageal pH, oesophageal manometry and fasting serum gastrin concentrations in 28 patients with reflux oesophagitis, before and during treatment with ranitidine 300 mg bd. Fourteen patients healed endoscopically at six weeks (group A) and 14 had residual oesophagitis (group B). Group A were characterised by a lower serum gastrin level before treatment (4.5±2 pmol/l; 2.4–10: mean and range) and group B (11.1±1 pmol/l; 3.5–21) and showed a marked reduction in acid reflux on treatment to near normal values. Mean % time below pH4 fell from 14.9 to 4.2 in group A (p<0.005) but was not affected in group B (14.2–15.6, not significant). Severity of reflux, degree of oesophagitis, lower oesophageal sphincter tone (Group A 27±8 mm Hg, group B 26±8 mm Hg), age, sex, smoking, obesity, duration or severity of symptoms were not significantly associated with healing. Abnormal peristalsis was common (29.4% abnormal waves, group A, 36% group B, NS) but did not inhibit the response to ranitidine, and did not improve with healing. Healing with H2 antagonists in oesophagitis is due to reduction in acid reflux, with no effect on oesophageal motility. The response cannot be predicted before treatment.

**Treatment of reflux oesophagitis with a prostaglandin analogue**

H I Smart, P D James, M Atkinson, and C Hawkey (University Hospital, Nottingham)
The prostaglandin analogue trimoprostil is gastro protective, inhibits acid secretion and does not reduce lower oesophageal sphincter tone. We therefore assessed its value in reflux oesophagitis.

Twenty patients received trimoprostil 750 μg qds and 22 received placebo in a one month double blind controlled clinical trial. Both groups were allowed antacids. Patients treated with trimoprostil (but not placebo) experienced a significant reduction in the frequency of pain, from seven (median, range 1–7) days/week (p<0.005) and in its duration, from two (1–12) to 0.5 (0–6–5) hours/day (p<0.02). Both groups reported a reduction in the severity of pain and sleep disturbance during the trial but differences between them did not reach statistical significance. There was a significant reduction in the extent of oesophagitis seen at endoscopy after treatment with trimoprostil from 5 (1–9) cm to 3 (0–9) cm (p<0.001). At the end of the trial eight patients taking trimoprostil showed no endoscopic evidence of oesophagitis.

Trimoprostil was well tolerated and appears to be an effective treatment for oesophagitis. Prostaglandins may be cytoprotective to the human oesophagus.

Ultrasound identification of oesophageal varices – comparison with endoscopy

S H SAYERMUTHU, A E A JOSEPH, AND J D MAXWELL (Departments of Medicine II and Ultrasound, St George’s Hospital and Medical School, London) Oesophageal varices are an important feature of chronic liver disease and are currently recognised by endoscopy or radiology. Because ultrasound is routinely used as the initial assessment of chronic liver disease the identification of oesophageal varices at this time would aid both investigation and management. We have attempted to directly visualise oesophageal varices by ultrasound examination of the lower oesophagus in a prospective comparative study with upper gastrointestinal endoscopy in 100 patients with suspected or proven liver or biliary tract disease. Oesophageal varices were recognised on ultrasound by thickening of the oesophageal wall and irregularity of the air containing lumen. In seven patients ultrasound was unable to adequately visualise the oesophagus while in four patients endoscopy was equivocal. Excluding these two groups ultrasound detected 18 of 22 oesophageal varices (sensitivity 82%) including all patients with medium or large varices while incorrectly suggesting varices in their absence endoscopically in six patients specificity 91%.

We conclude that ultrasound can identify oesophageal varices with high sensitivity and specificity and should be specifically examined for in all patients with suspected chronic liver disease.

Prospective controlled trial of propranolol and sclerotherapy for prevention of rebleeding from oesophageal varices

C VICKERS, J RHODES, P HILLENBRAND, H BRADBY, P HAWKER, P DYKES, I CHESNER, R COCKEL, D ADAMS, R VALORI, J DAWSON, H O’CONNOR, AND E ELIAS (Queen Elizabeth, Good Hope, General, Selly Oak, East Birmingham, and Sandwell Hospitals, Birmingham) Sclerotherapy is of value in the treatment of acute variceal haemorrhage although rebleeding occurs in up to 55% of patients. We have evaluated the role of additional longterm propranolol to further reduce the rebleeding rate and improve survival. Sixty nine patients (41 M), admitted with bleeding varices to a district hospital, were randomised to receive regular sclerotherapy, plus propranolol 160 mg (long acting) (n=35) or placebo (n=34). Median follow up was 96 and 110 weeks respectively (range 44–233). Both groups were similar for age, sex, aetiology, and Child’s grading.

Interim analysis on intention to treat, 55% of propranolol and 71% of placebo treated patients were free of rebleeding (p=NS). Median time to rebleeding was 15 weeks (1–130) in the propranolol and nine weeks (1–94) in the placebo group. There were 22 deaths (propranolol 13) with rebleeding responsible in 13 (propranolol nine). Cumulative per cent survival was 58% in the propranolol and 72% in the placebo group (p=NS).

The results show that in patients undergoing regular sclerotherapy after an episode of variceal haemorrhage, longterm propranolol confers no additional benefit in survival or prevention of variceal rebleeding.

Interdigestive gall bladder emptying and its relationship to motor activity in man

S ELLENBOGEN, J S GRIME, J CALAM, C R MACKIE, S A JENKINS, AND J N BAXTER (Department of Surgery, University of Liverpool, Department of Nuclear Medicine, Royal Liverpool Hospital, Dept of Gastroenterology, Royal P G Medical School, London) Human gall bladder emptying (GBE) occurs during both digestive and interdigestive periods. The mechanism for interdigestive GBE is unknown but may be related to the intestinal migrating motor complex (IMMC) (fasting cyclic and phasic intensity activity). Using "Tc"-EHIDA cholescintigraphy and gastrointestinal manometry, interdigestive GBE and the
IMMC were observed in two groups of healthy volunteers; group I, observed for 134–298 minutes without stimulation (n=18); group II, observed for 90 minutes after atropine (0-6 mg +0-3 mg/kg/h) (n=8). In group I, 17 complete IMMC cycles were recorded. The cycle length was 100±15-5 minutes, and the lengths of the phases were: phase I, 35±3±6-6 minutes; phase II, 60±6±10-4 minutes; and phase III, 5±2±0-3 minutes. Interdigestive GBE occurred on nine occasions; four during phase I, and five during phase II. In 10 of the IMMC cycles, GBE did not occur, whilst in two cycles GBE occurred twice. The relationship between spontaneous GBE and the phases of the IMMC was random (p<0.25; χ² goodness of fit). The gall bladder emptied 18±±0-4% of its contents (mean±SEM). From group I, the probability of GBE in any minute period was calculated as 0.0053. Atropine inhibited GBE in all eight group II volunteers during the 90 minute study period (p<0.001, Poisson test, group II v group I).

These results suggest that interdigestive GBE (1) occurs infrequently and in small volume, (2) is unrelated to the phases of the IMMC, (3) is cholinergically mediated.

Bile lipid and gall stone (GS) dissolution responses to combined chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA) treatment

K HOOD, D GLEESON, G M MURPHY AND R H DOWLING (Gastroenterology Unit, Guy’s Campus, University of London, UK) Oral CDCA dissolves radioopaque GS with moderate efficacy but causes dose related diarrhoea and hyper-transaminasaemia. Ursodeoxycholic acid is free from these side effects but has lower efficacy, in part because of acquired GS calcification. To minimise side effects whilst maintaining efficacy, we gave 7.5 mg CDCA plus 5 mg UDCA kg/day (half normal doses) to 34 patients (6 M, 28 F) aged 23–91 (median 51) yr with radioopaque GS measuring 8.7±SEM 0.9 mm max diam in ‘functioning’ gall bladders. Biliary chol satn index (SI), measured in 15, fell from 1.1±0.09 before (SI<1.0 in five suggesting non-chol stones) to 0.8±0.06 after six weeks treatment. Fourteen were treated <6 mo (surgery in four, default in three, three to five months treatment in seven). Of 20 followed >6 mo, three showed complete and five partial GS dissolution corresponding to 44±12.5% at one year by life table analysis. Two patients showed no response at six months but partial GS dissolution at 12 months. No patients with suspected non-chol stones responded to treatment. There were no abnormalities of liver function or serum lipids and no acquired GS calcification but 11 had diarrhoea – transient in four, but requiring CDCA dose reduction in five and withdrawal in two.

(1) Pretreatment SI <1.0 predicts lack of response. (2) CDCA+UDCA have lower efficacy (44±12.5% at one year) but few side effects than single bile acids. (3) Withdrawal of treatment for non-response should be delayed until one year.

In vivo cholecodocholitholysis using methyl tertiary butyl ether (MTBE)

G A LAFERLA, G FULLERTON, AND W R MURRAY (University Department of Surgery, Western Infirmary, Glasgow) The management of choledocholithiasis has been revolutionised by endoscopic sphincterotomy. Stone extraction through the sphincterotomy is limited by their size. If extraction fails a nasobiliary catheter (NBC) can be placed endoscopically thus allowing access to the stones for dissolution therapy. We present our preliminary experience using the aliphatic ether MTBE. Ten patients (eight men, two women; age range 65–85 years) with suspected choledocholithiasis were referred for ERC, six having previously undergone cholecystectomy. Endoscopic cholangiography confirmed multiple (2–12) large stones (diameter 15.0 mm–27.5 mm). Post sphincterotomy extraction failed in all cases. An NBC was inserted and 24 hours later MTBE dissolution was commenced using 2–5 ml of the solution every 30 minutes over a two hour period. An average of four dissolution sessions were performed per patient. Subsequent stone assessment revealed complete disappearance in three patients, significant reduction in stone size allowing subsequent duct clearance in five patients and no change in two. Complications noted were mild drowsiness (one patient) and nausea (one patient). Minor transient abnormalities in liver function tests occurred in all patients. This effective agent, which has a low morbidity is of value in the management of the frail and elderly patients with large bile duct stones.

Stone extraction after endoscopic sphincterotomy – and active policy is best

D F MARTIN, J C McGregor, M E LAMBERT, AND D E E TWEEDIE (Gastrointestinal Unit, University Hospital of South Manchester, West Didsbury, Manchester) In order to evaluate a policy of primary stone extraction after endoscopic sphincterotomy (ES), we have reviewed the success and complications of this procedure in 262 patients seen between January 1981 and December 1985. In 85 patients whose bile ducts were cleared of stones immediately after ES, acute pancreatitis developed in three (3.5%) and another (1.2%) died from a pancreatic abscess after admission with acute pancreatitis. None developed any other complication. In 177 patients whose stones were not cleared, 56 had insertion of a pernasal catheter. Eight of these (10.2%) developed complications, two (3.4%) of which were cholangitis related to tube blockage or displacement. In the remaining 121 patients, stones were left without drainage. Complications developed in 18 (15.2%) but eight of these had bleeding.
which precluded attempts at extraction. Four patients (3-3%) developed cholangitis and another (0-8%) cholecystitis despite intravenous antibiotics. Two patients (1-6%) died. Although development of complications of ES, particularly bleeding, may lead to failed duct clearance, it appears that infective complications are more likely when duct clearance fails. An active policy of primary stone extraction with the use of pernasal catheters or stents when this fails, may be expected to reduce the risk of cholangitis.

Can videoproctography and anorectal physiology predict outcome after rectopexy for the solitary rectal ulcer syndrome (SRUS)?

I G Finlay, C J Bartram, and R J Nicholls (St Mark's Hospital, City Road, London) Anterioposterior rectopexy improves some patients with SRUS without external prolapse. We have carried out preoperative videoproctography and anorectal physiology in 17 such patients in an attempt to predict the outcome of surgery. Postoperatively 12 (group A) were improved symptomatically and five (group B) were not. Videoproctography showed complete rectal emptying within 30 seconds in nine patients and incomplete emptying in three patients, in group A. All five patients in group B had incomplete emptying (p<0-05). Perineal descent, estimated in 14 patients, was found in 4/9 in group A and 5/5 in group B (p<0-05). Internal prolapse was found in 6/12 patients in group A and 5/5 in group B (p<0-08, NS). Eleven of the 13 patients without paradox were in group A.

There was no significant difference between basal/squeeze anal canal pressures (group A 96±14 mm Hg/65±16 mm Hg, group B 77±18 mm Hg/70±10 mm Hg) and the rate of rectal emptying estimated by videoproctography in six patients in each group (p=0-17). Intact patients were found in 4/9 in group A and 5/5 in group B (p<0-05). Internal prolapse was found in 6/12 patients in group A and 5/5 in group B (p<0-08, NS). Eleven of the 13 patients without paradox were in group A.

Consumer guide to anal manometry: a comparison of microtransducer, water and air filled microballoon systems

R Miller, D C C Bartolo, A M Roe, N J MCC Mortensen, and D James (Department of Surgery, Bristol Royal Infirmary, Bristol and Department of Clinical Measurement, Royal Devon and Exeter Hospital, Exeter, Devon) Water filled microballoon manometry systems have many disadvantages and microtransduer tipped catheters (MTC) have been advocated as reliable alternatives. Maximum resting (MRP) and maximum voluntary contraction (MVC) pressures were compared using the two systems with a standard station pull through technique in 12 patients. There was poor correlation (MRP r=0.62 p<0.05, MVC r=0.42 p<0.05). To determine whether this was because of MTC radial pressure variation we studied 39 patients with both systems, recording pressures from each of four quadrants with the MTC. Improved correlation was found (MRP r=0.72, MVC r=0.87 p<0.001). Repeated MTC measurements was a laborious process and we therefore compared a new air filled microballoon system with the water filled system in 44 patients with an excellent correlation (MRP r=0.86 p<0.001 and MVC r=0.94 p<0.001). Repeated studies in 10 patients showed good reproducibility (spinehter length r=0.95, MRP r=0.98, MVC r=0.89).

Anorectal sensation: its role in the continence mechanism

R Miller, D C C Bartolo, F Cervero, and N J MCC Mortensen (Dept of Surgery, Bristol Royal Infirmary, Bristol and Dept of Physiology, University of Bristol, Bristol) To elucidate the role of sensation in the continence mechanism we studied mucosal electrosensitivity (ME) and temperature sensation in the lower, mid and upper thirds of the anal canal in 40 control patients (age 43, 18–83)*, 24 with incontinence (age 57, 34–80)* and 20 with haemorrhoids (age 55, 23–77)*. A small electric current passed between two electrodes 1 cm apart on a catheter measured ME in millivolts and a water perfused thermode 1 cm long was used to measure the minimum detectable temperature change (MDTC) in °C. The incontinent group had a severe sensory deficit in all zones and the haemorrhoid group in general had a milder sensory loss (control/haemorrhoid/incontinent: ME (mv): lower 4.0±3.7/0±0, middle 4.0±5.5/ 8.0*, upper 5.5±12.0/11.5*, MDTC °C: lower 0.8±1.2/2.2*, middle 0.9±1.2/2.2*, upper 1.0±3.1*/>4.5*).

We believe that impaired anal sensation may be an important contributory factor to the pathogenesis of faecal incontinence. Lesser degrees of sensory loss related to haemorrhoidal prolapse is not associated with incontinence in the presence of good sphincter function.

The sampling reflex: a comparison of normal and incontinent patients

R Miller, D C C Bartolo, F Cervero, and N J MCC Mortensen (Department of Surgery, Bristol Royal Infirmary, Bristol and Department of Physiology, University of Bristol, Bristol) To investigate the concept of anorectal sampling we studied 18 patients with faecal incontinence and 18 age and sex matched controls. A multichannel microtransducer catheter was positioned so that pressures were recorded from the rectum and the junction of the mid and upper thirds of the anal canal. Resting pressures were recorded for five minutes and whilst distending the rectum with 10 ml increments of air injected into a small latex balloon, and then freely into the rectum. Sampling, (equalisation of rectal and upper anal pressures), occurred spontaneously in 16 of the controls and only six of the incontinent group (p<0.02, x² test). Induced sampling occurred at a higher rectal volume in the incontinent group for freely injected air (control: 10 ml [10–70 ml], incontinent 40 ml [10 ml–>100 ml]) p<0.002, Mann–Whitney U test). There was no difference for air injected into the balloon (control 20 ml [10–70 ml], incontinent 20 ml [10–70 ml]).

We believe this defective sampling response may be a significant contributory factor in the pathogenesis of faecal incontinence, preventing sensory discrimination of rectal contents. (a=median, range.)

Defecographic findings in young healthy volunteers

P J Shorvon, F Mchugh, S Somers, and G W Stevenson (Department of Radiology, McMaster University, Hamilton, Canada and Department of Medicine, Toronto...
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University, Canada) As previous reports on defecography suffer from the absence of data on normal subjects, we recruited 48 healthy young adult student volunteers (25 men and 23 women) to undergo a defecogram. For the procedure, after coating of the rectal mucosa with liquid barium, a barium paste was inserted into the rectum. The external anal orifice was marked with barium ointment, and women inserted a contrast soaked vaginal tampon. Video fluoroscopic recordings in the lateral position with 100 mm spot films were taken at rest, with contraction of pelvic muscles, on straining and during defecation. Twenty variables were measured directly using a centimetre midline scale. Ten radiographic appearances were also recorded and graded.

The results indicate the range of normality to be much wider than previously realised; for example 44% of men and 45% of women had a high grade intussusception, 77% of women had an anterior rectocele (moderate to large in 9/23). The mean pelvic descent from rest in women was 2.0 cm and greater than 3 cm in 23%. In men the mean was 1.9 cm, with 20% greater than 3 cm. Four subjects had an open anal canal at rest with apparent incontinence. Caution must be exercised in overinterpreting defecograms of patients.

Physiology of defecation – the importance of the levator ani muscles

I G Finlay, K Carter, and I McIloot (introduced by D C Carter) (University Dept Surgery, Royal Infirmary, Glasgow) Coordinated relaxation of the puborectalis/anal sphincter muscles resulting in an obtuse anorectal angle is necessary for unobstructed defecation. The factors which initiate this mechanism are unknown. We used videoproteography, micropressure transducers and EMG to simultaneously study anorectal angle, intrarectal/anal canal pressures and external sphincter/puborectalis/levator EMG in five normal patients. The cuff to stool was initiated by the instillation of 180 ml barium (1:25 mg/ml) over a 120 second period. Observations were made during the instillation and voluntary expulsion of barium.

The instillation of barium produced (a) a mean fall in anal canal pressure from 40±16 mm Hg (mean±SE) to 13±8 mm Hg. (b) A rise in intrarectal pressure from 0 to 30±5±12 mm Hg. (c) An increase in anorectal angle from 86±7 degrees to 103±7 degrees at the call to stool and 115±5 at 120 seconds. EMG showed no change in puborectalis/anai sphincter activity during the instillation of barium. Expulsion of barium was achieved by further increasing anorectal angle to 134±5 degrees and decreasing anal canal pressure to zero mm Hg as a consequence of abolition of puborectalis/external sphincter EMG activity. These results suggest that elevation of the levator ani occurs before relaxation of the puborectalis during defecation. Failure of this coordinated activity may be the basic abnormality in patients with symptoms of obstructed defecation.

Does the position of the patient influence the results of anorectal manometry?

K Yoshoka, V Pinson, and M R B Keighley (Surgical Department, The General Hospital, Birmingham) We have compared measurement of pressures at 2, 4, and 26 cm from the anal verge using an open tipped perfused catheter in three groups of patients: controls (n=11), constipation (n=21) and incontinence (n=14). Pressures were measured at rest (R), during maximum pelvic floor contraction (S) and attempted defecation (St) in the left lateral (LL) and seated position (S). No significant difference between the seated and lateral position was observed at 2 cm in all groups. At 4 cm, there was no significant difference in control group, whereas significant differences were observed in the group of patients with incontinence (R:p<0.025, Sq:p<0.025) and the group of patients with constipation (R:p<0.025, St:p<0.05). At 26 cm pressures were significantly greater in the seated position for patients with incontinence (R:p<0.01, Sq:p<0.01). Compliance (ml/cm H20) did not differ significantly with position in controls (LL=8.48, S=13.08), incontinence (LL=14.82, S=16.34) or constipation (LL=10.97, S=11.77). Measurement in the left lateral position is unphysiological and differs significantly from the seated position particularly in incontinent patients.

Physiological parameter should dictate the surgical management of longstanding idiopathic chronic constipation

K Yoshoka and M R B Keighley (Surgical Department, The General Hospital, Birmingham) We have found that idiopathic longstanding constipation may be due to outlet obstruction (OO) as shown by failure to evacuate rectal contents on proctography or by electromyographic evidence of increased puborectalis activity on attempted defecation (n=26). Alternatively, patients may have colonic inertia (CI) as demonstrated by failure to achieve an increased motility index after rectal bisacodyl or where passage of radio opaque markers is delayed (n=4). Some patients have both OO and CI (n=10). Anorectal myectomy (ARM) gives good results in patients with OO whereas subtotal colectomy is reserved for patients with CI. We have reviewed the results of ARM for OO with normal transit (60%–100% marker passed in five days) and those with OO and/or CI (less than 60% markers passed five days). ARM achieved passage of at least three stools per week without laxative in 10 of 12 patients (83%) with OO who have normal transit compared with only eight of 16 patients (50%) with OO and/or CI. Six patients with OO and/or CI have subsequently required subtotal colectomy which restored bowel habit to normal in five patients (83%) and none developed incontinence after a previous ARM.

Clinical and physiological evaluation of postanal repair

K Yoshoka, G Hyland, and M R B Keighley (Surgical Department, The General Hospital, Birmingham) Postanal repair (PAR) is used for treatment of idiopathic faecal incontinence (IFI) on the premise that it restores a deficient anorectal angle. We have reviewed the long term results of PAR in 124 patients between 1976 and 1986. We have measured anal and rectal pressures, rectal compliance, anal and rectal sensation and performed proctograms before and three months after operation (n=9).

Results are compared with age and sex matched controls. Only 24% (34%) of the 79 patients followed for more than three years claimed complete continence. Although 50% (69%) were improved, soiling occurred in 43 (62%) and 40 (56%) continued to wear pads. Resting (R) and squeeze (S) anal canal pressures were significantly lower in IFI than controls (R:49±7 v 83±0, p<0.01, S:77±2 v 130±9, p<0.005) there was no significant improvement in anal pressures after PAR (R before and after: 49±7 v 47±3, S before and after: 77±2 v 69±1, NS).

Furthermore there was no objective improvement in anal sensation (lower zone before and after PAR: 137 mA and 144 mA, 10.1136/gut.28.10.A1328 on 1 October 1987. Downloaded from http://gut.bmj.com/ by guest. Protected by copyright.
The British Society of Gastroenterology

NS). The resting anorectal angle was significantly more obtuse in IFI than controls (130-6 v 114-1, p<0-025) but PAR had no influence on resting angles (pre and post: 130-6 v 131-8, NS). Although intestine patients have obtuse anorectal angle post anal repair was associated with no physiological change and results were disappointing.

Action of cisapride on intractable constipation associated with spinal and pelvic nerve injury

N R BINNIE, P EDMOND, AND A N SMITH (Spinal Injuries Unit and Gastro-intestinal Unit, Western General Hospital, Edinburgh) Interruption of the parasympathetic nerves to the colon, in the spinal canal or in the pelvis, results in lessened colonic motility and constipation. Simulating nerve stimulation by the release of ACH at the myenteric plexus should correct the colonic dysmotility. Cisapride releases ACH at the myenteric plexus. Oronal transit time (OATT) has been studied in 15 patients who related the onset of their constipation to the time of spinal cord injury (n=10) or pelvic surgery for hysterectomy (n=5), before and after oral administration of cisapride. During the study each patient acted as his/her own control. Before cisapride, both groups of subjects showed delayed OATT (spinal group 187±87 hours, hysterectomy group 130±167 hours) the passage of the ‘Hinton markers’ as a bolus in 1-7±0-5 stools. With cisapride there was a significant reduction in OATT (spinal group now 125±73 hours; hysterectomy group 81±31 hours) and the markers passed in 3-2±1-4 stools. The motility effect is predominantly on the colon as the small bowel transit was 3-2±1-3 hours before and after cisapride 2-8±0-7 hours. Faecal water content in stool specimens remained unchanged (62-5% and 63%).

Stimulation of anterior sacral nerve roots in man: the proximal extent and differential effects on colonic motility

N R BINNIE, P EDMOND, G H CREASY, AND A N SMITH (Spinal Injuries Unit and Gastro-intestinal Unit, Western General Hospital, Edinburgh) Brindley introduced sacral anterior root stimulators for bladder control in paraplegic subjects. Their effects on colon function have since been studied in spinally injured man. The present study ascertains the nature and proximal extent of the motility response to sacral nerve root stimulation in six male paraplegic subjects. With endoscopic access, pressure recordings were taken from the transverse colon and continued distally using conventional manometric methods. There was a pressure increase in response to S2 and S4 (15±10 cm of water) but S3 stimulation caused the greatest pressure response (45±20 cm of water). This response affected all of the left colon but in three subjects began 10 cm proximal to the splenic flexure confirmed radiologically. In the lower left colon the motor responses were peristaltic propagated distally between three pressure transducers in series. This study establishes that the extent of colonic motor response to sacral root stimulation extends from or even proximal to the splenic flexure and suggests that the S3 root is the dominant spinal nerve root for elicitation of motility responses in the left colon.

Combined sensorimotor deficit in primary neuropathic faecal incontinence

J ROGERS, J J MISIEWICZ, AND M M HENRY (Department of Gastroenterology, Central Middlesex Hospital, London) Patients with idiopathic faecal incontinence (IFI) often report that they have no sensation of impending or actual incontinence. We have studied 11 patients with IFI, eight women, mean age (±SD) 56±2±16-9 yrs and nine normal controls (NC), four women, 56±6±15-9 yrs with techniques of mucosal electro-sensitivity (MES) and rectal distension for the descriptive assessment of anorectal sensation. Pelvic floor motor function was assessed by calculating fibre density (FD) from single fibre EMG’s of the external anal sphincter; pudendal nerve terminal motor latency (PNTML); and anal canal manometry.

Mucosal electrosensitivity showed a significant (0-001<p<0-02) sensory deficit in the upper, 18-4 (5-2-25) mA, median (range) v 5-3 (3-9-6-9); middle, 10-1 (5-7-21-4) v 3-7 (1-7-7-2); and lower, 8-9 (3-1-21-6) v 4-4 (3-1-6-0) thirds of the anal canal in IFI compared with controls. Fibre density and PNTML were significantly increased in IFI compared with controls [1-73 (1-2-2-18) v 1-38 (1-06-1-69), p<0-05 and 2-5 (1-90-3-15) ms v 1-95 (1-75-2-15), p<0-002], indicating a motor-neuropathy. There was a concomitant decrease in anal canal manometry [resting pressure: 40 (40-120) cm H2O v 100 (40-120), p<0-05; squeeze pressure: 60 (0-120) cm H2O v (100-210), p<0-002]. Rectal sensation was similar in both groups. This is the first report of a significant sensory deficit in the anal canal in combination with a motor neuropathy in a group of patients with primary neuropathic faecal incontinence.

Sensorimotor pelvic floor neuropathy: a comparison of diabetes mellitus and idiopathic faecal incontinence

J ROGERS, J J MISIEWICZ, AND M M HENRY (Department of Gastroenterology and Nutrition, Central Middlesex Hospital, London) Diabetic neuropathy is common, but pelvic floor function has not been investigated in this condition. We studied 21 diabetics (DM), mean age (range) 55-3 (36-72) years, 18 patients with idiopathic faecal incontinence (IFI), 54-1 (25-83) years and 11 age matched controls. All diabetics had peripheral sensory neuropathy but none had faecal incontinence. Pelvic floor motor function was assessed by calculating fibre density (FD) from single fibre EMG of external anal sphincter; pudendal nerve terminal motor latency (PNTML); and anal canal manometry. Sensation was assessed by balloon distension of the rectum and mucosal electro-sensitivity (MES) of the anal canal. FD was significantly (p<0-01) increased in DM and IFI compared with controls [median (range): 1-82 (1-42-2-57) and 2-67 (1-21-2-37) v 1-38 (1-06-1-60), respectively]. Mucosal electrosensitivity showed a significant (p<0-01) sensory deficit in the upper, middle and lower thirds of the anal canal in DM and IFI compared to controls, [8-2 (3-1-13-5) mA and 11-2 (5-2-25) v 5-3 (3-4-6-9); 6-2 (2-7-10-7) and 7-0 (2-1-21-4) v 3-7 (1-7-7-2); 6-2 (2-9-17-5) and 5-7 (8-2-21-6) v 4-0 (2-0-6-2), respectively]. Pudendal nerve terminal motor latency and manometry were similar to controls in DM. In IFI PNTML significantly (p<0-01) increased [2-50 (1-80-3-15) ms v 1-95 (1-7-2-25)], and manometry decreased [resting pressure: 40 (20-120) cm water v 90 (40-120), squeeze pressure: 40 (0-160) v 140 (50-210)]. Rectal sensation was similar in all groups. This asymptomatic sensorimotor pelvic floor neuropathy is a new finding in DM and is in contrast with the symptomatic neuropathy of IFI.

Rectal prolapse, anterior mucosal prolapse, solitary rectal ulcer. Are they caused by rectal herniation through a weak sphincter?
A histopathological study of severe constipation

N D HEATON, P KLUCK, J R GARRETT, AND E R HOWARD (King's College Hospital, Denmark Hill, London and Dept Cell Biology and Genetics, Erasmus University, Rotterdam, Holland) Resection specimens from 20 patients with severe constipation (mean age 14 years; male:female 11:9) not responding to medical treatment and who had a partial or subtotal colectomy were examined histochemically (simple hydrolyses to identify neurones; nerves assessed for cholinesterase activity and catecholamine fluorescence), and immunocytochemically for anti-neurofilament antibody. Four distinct histochemical patterns were recognised - 'normal' (seven patients), aganglionosis (two), hypoganglionosis (six), and hyperganglionosis (five). Neurofilament 'staining' identified four patterns of immunoreactivity - 'normal' (three patients), aganglionosis (two), hyperganglionosis (one), and 'constipated' (14). There was close correlation between the two methods for recognising abnormal colonic innervation. Four of the seven patients, however, with a normal histochemical appearance (all slow colonic transit) had abnormal neurofilament 'staining'. The histopathological appearance at the resection margin related to the clinical outcome. The combined use of these two techniques on resection specimens from patients with chronic constipation identifies more subtle abnormalities of colorectal innervation than routine histological methods.

Experience of lateral puborectalis division for severe constipation

M A KAMM, P R HAWLEY, AND J E LENNARD-JONES (St Mark's Hospital, City Road, London) Patients with severe constipation often do not 'relax' their pelvic floor during defaecation. Lateral division of the puborectalis and upper external sphincter muscles was performed in an attempt to restore defaecatory function in a group of these severely constipated patients. The operation was carried out in 18 patients, all women. Mean age was 32. Patients with Hirschprung's disease and secondary causes of constipation were excluded. Fifteen patients had severe idiopathic constipation with normal barium enema, and three patients had a megarectum or megacolon and sigmoid. The operation was performed unilaterally in 12 and bilaterally in six; three patients had the operation performed twice (on the same side).

Three patients reported symptomatic improvement (one bilateral, two unilateral...
The normal colon is therefore capable of generating high pressure peristaltic waves which correlate with effective transport of colonic contents. There was a clearly definable abnormality in all the patients. Assessment of colonic transit in response to a standard chemical stimulus enables the delineation of functionally abnormal regions.

Discrimination is not impaired by excision of the anal transitional zone after restorative proctocolectomy and ileo-anal anastomosis

M R B KEIGHLEY and M C WINSLET (The General Hospital, Birmingham) The anal transition zone (ATZ) is richly innervated by sensory nerve endings and is often not involved in ulcerative colitis. It has been suggested that the ATZ should be preserved in patients having restorative proctocolectomy and ileoanal pouch anastomosis. We have studied eight patients before and after ileoanal pouch anastomosis to determine the influence of excising the ATZ on anal sensation and ability to discriminate gas from solid stool postoperatively. Anal sensation was measured in the anal high pressure zone as defined by manometry using a unipolar constant current stimulator. The median threshold sensation in the lower zone of the anal canal postoperatively was 62 mA compared with 134 mA preoperatively (p<0.02). Mid zone and upper zone threshold values had a median of 67 mA and 77 mA preoperatively but sensation was unrecordable (>150 mA) after restorative proctocolectomy (p<0.01). Despite the objective loss of sensation in the upper anal canal, only one of the eight patients was unable to discriminate gas from semisolids stools three months after operation, soiling was reported in only one patient, none were incontinent and all were able to defecate for more than one hour. Although the excision of the ATZ impairs anal sensation, functional results do not appear to be impaired.

Factors influencing the outcome of restorative proctocolectomy

MC WINSLET, R FLNN, and M R B KEIGHLEY (The General Hospital, Birmingham) Factors influencing the outcome of restorative proctocolectomy in 40 patients followed up for a median of 20 (6–46) months has been assessed by univariate and multivariate analysis. The variables assessed included age, sex (F=21), previous colectomy (n=15), covering ileostomy (n=35), rectal cuff preservation (n=13), endoanal mucosectomy (n=15), type of pouch (S=1, W=8, J=31), diagnosis (UC=30, polyp=3, megarectum=4, Crohn’s disease=3), vascular mobilisation (n=20), experience (last 20 cases), and complications: pelvic sepsis (n=12), anal stenosis (n=9), fistula (n=8), obstruction (n=6). Failure was defined as pouch excision intubation or continued proximal stoma (n=9). The complication score (0–8) included: bleeding, sepsis, stenosis, fistula and obstruction. The functional score (0–12) assessed frequency, use of pads, urgency, soiling, incontinence, discrimination, use of anti diarrhoeals and dietary restriction. Failure occurred in two patients.
with Crohn’s disease and seven with ulcerative colitis and was significantly more common after endo-anal mucosectomy (53% v 4%, p<0.01), rectal cuff preservation (46% v 11%, p<0.05), and pelvic sepsis (37% v 4%, p<0.01). The complication score was only increased after endoanl mucosectomy (3 v 0, p<0.05). Only pelvic sepsis (10 v 1, p<0.01) and fistulae (10 v 1, p<0.05) influenced the functional score. Hospital stay was significantly prolonged after preserving the rectal cuff (39 ±23 days, p<0.05), endoanal mucosectomy (40 ±23 days, p<0.01), pelvic sepsis (48 ±23 days, p<0.01), and fistulae (49 ±24 days, p<0.05).

Segmental colonic transit in ulcerative colitis – effect of Asian versus Caucasian diet

R C Spiller, H H Tay, D B A Silk, and J J Miseiwicz (Department of Gastroenterology, Central Middlesex Hospital, Acton Lane, London) Recent reports that proctitis is associated with delayed colonic transit have not allowed for the known effect of dietary fibre. In the present study segmental colonic transit, three day stool weights and fibre intake have been assessed in 26 patients, 14 with proctitis, 11 with proctocolitis. Ten were taking an Asian and 16 a Caucasian diet. There was no difference between the two diet groups in sex ratio or disease distribution and activity as assessed endoscopically. Twenty radioopaque pellets were ingested at 900 am on days 1–3. Mean transit in hours was 1.2 ±2 (the number of pellets seen within each segment on a radiograph taken at 900 am on day 4.

Patients taking a traditional Asian diet had larger stool weights, 278±19 g/24 h, (mean ±SEM) n=10, compared with those taking a Western diet, 100±1 g, n=16, p<0.01. Total colonic transit was correspondingly faster (12±6 ±3±3 h, p<0.01), correlating inversely with stool weight, r=0.56, p<0.01. The difference in fibre intake (28±4 ±20±2 g) was not significant suggesting that other factors –– for example, spices are responsible for the accelerated colonic transit. The extent of disease per se did not influence transit. The difference in transit between active (12±6±3±2 h, n=10) and inactive disease (31±4±3±2, n=20) was, however, not significant. Thus in our patients diet appears to have a more powerful influence on colonic transit than their disease.

Mechanisms of transport of sodium and chloride and the effects of short chain fatty acids in the human infant colon

H R Jenkins, U Schrackenberg, and P J Milla (Institute of Child Health, London) A major function of the colon is the conservation of salt and water which may be aided by short chain fatty acids. The only previous studies of the mechanisms involved in infants have been in vivo where electrical gradients influence ionic movements. We have carried out a more detailed study of transport in isolated human infant colon using a Ussing Chamber and voltage clamp procedure. Stripped L side colonic mucosa (n=6 pairs) was mounted and bathed in Krebs solution. Under short circuit conditions Na⁺ (3-45±1.53 μmol/h/cm² mean ±1SD) and Cl⁻ (0-63±3-61) were absorbed and a residual ion flux consistent with HCO₃⁻ secretion approximates C₁⁻ absorption. Short circuit current (3-8±0-28) approximates net Na⁺ movement. Sixty millimoles acetate increased Na⁺ absorption (3-45±1-53 to 7-74±2-25, p<0.05) by a large increase in mucosa to serosa flux (7-24±0-92 to 13-55±1-62, p<0.01). The increased net absorption of Na⁺ was markedly reduced by 10⁻⁴ M amiloride (7-74±2-25 to 1-75±1-72, p<0.01) which was also associated with a marked reduction in tissue conductance. These data clearly show that in the infant Na⁺ is absorbed electrically and Cl⁻ electroneutrally in exchange for HCO₃⁻ unlike in vivo where Cl⁻ moves according to the electrical gradient. Short chain fatty acids favourably influence Na⁺ saliva and do so via the amiloride sensitive Na⁺ channel. Thus bacterial metabolism of carbohydrate in the infant colon may be important in the conservation of salt and water.

Breath hydrogen monitoring in Pneumatosis coli

M Schlup, G O Barbezat, and V S Chadwick (Department of Medicine and Wellcome Institute, University of Otago, Dunedin, New Zealand) Intestinal gas producing bacteria have been implicated in the pathogenesis of Pneumatosis coli. Previous reports of high hydrogen (H₂) content within cysts and breath of some patients prompted us to investigate two female patients (aged 57 and 47 years) with colonic pneumatosis coli presenting with tenesmus and rectal bleeding. In both patients mean fasting breath H₂ concentrations were raised: 75 ppm (range 65–87) and 49 ppm (41–54). A bowel lavage (Golytely, 4 L in four hours) reduced breath H₂ from 65 ppm to 15 ppm and from 42 ppm to 10 ppm within 12 hours. Subsequent treatment for seven days with an elemental diet (Ensure, 1500 KCal/d) supplemented by Golytely 2 L/d in one patient and activated charcoal 20 g/d in the other patient resulted in persistently low breath H₂ with a mean of 13 ppm (3–38) and 12 ppm (5–21) as shown by daily breath H₂ monitoring. Symptoms improved and sequential plain abdominal films showed virtually complete regression of cysts.

This well tolerated treatment resulted in a marked reduction of H₂ production probably by depriving H₂ producing bacteria of substrate. We assume that this reverses concentration gradients from cyst to bowel resulting in disappearance of the cysts.

COLORECTAL II

Colonic cellular proliferation rates in normal subjects: the effect of the faecal stream

M Winslet, A Allan, Denise Youngs, and M R B Keighley (The General Hospital, Birmingham) The role of the faecal stream in maintaining colonic mucosal cellular kinetics was assessed by measuring the cell birth rate (cyst cell production rate – CCPR) of normal rectal mucosa in 10 patients undergoing faecal diversion by ileostomy for incontinence (n=6) or protection of an anastomosis (n=4). Rectal biopsies were obtained before diversion and two, six, and 12 weeks afterwards. The effect of restoration of intestinal continuity was assessed at the same time points in nine patients undergoing closure of ileostomy (post incontinence procedure n=4, post anastomotic protection n=5) CCPR was assessed by an in vitro stathmokinetic method with vincristine induced metaphase arrest. Faecal diversion was associated with a significant fall in CCPR from 3-4±1·0 to 1-2±0-4 at two weeks, p<0.05. The CCPR subsequently increased to 1-7±0·4 at six weeks. and 3-3±1·5 at 12 weeks. Restoration of intestinal continuity was not associated with a significant change in CCPR. Faecal diversion causes a significant transient reduction in rectal CCPR. These data suggest that the faecal stream has a tropic effect on mucosal cellular proliferation. The mechanism of this phenomenon is unclear.

Effect of dietary fibre supplementation on colonic pH in healthy volunteers

G Pye, J Crompton, D F Evans, A G Clarke, and J D Hardcastle (Department of...
Role of in vivo $^{99m}$technetium labelled red blood cell scintigraphy in lower gastrointestinal haemorrhage

J F SHARP, J P NEOPTOLEMOS, M NICHOLSON, E M WATKIN, AND D P FOSSARD (Departments of Surgery and Radiology, Leicester Royal Infirmary and Leicester General Hospital, Leicester) Twenty eight patients with major rectal bleeding had in vivo $^{99m}$technetium pertechnetate (395–590 mBq) labelled red cell scintigraphy in an attempt to identify the haemorrhage site. Serial scans (0–35 hours) were taken using a large field gamma camera (10$^6$ counts).

Three patients were children. There were 17 male and eight female adults, mean age 72-4 years (range 51–91 years). The average haemoglobin at presentation was 9.5 g/dl (range 5.4–13.5 g/dl). The mean transfusion was 8-2 units (range 3–20).

Twenty nine scans were performed; 22 were positive and in all these the site of haemorrhage was identified either during the episode of bleeding (n=14) or subsequently (n=8). The bleeding site was confirmed by colonoscopy, arteriography or at laparotomy. Seven patients had negative scans, no bleeding sites were found but two patients subsequently had colonoscopic polypectomy. On average after admission positive scans were performed earlier 4-3 days (range 0-5–14 days) than negative scans 6-7 days (range 1–14 days).

$^{99m}$Technetium scintigraphy is a useful procedure and has a high diagnostic yield. It allows preoperative identification of bleeding sites and should be used early when bleeding is still occurring.

Left sided colonoscopy as screening procedure for colorectal neoplasia in asymptomatic volunteers ≥45 years

D F FOLEY, P DUNNE, M O'BRIEN, J CROWE, T W O'CALLAGHAN, AND J R LENNON (Louth Hospital, Dundalk, Depts of Gastroenterology and Pathology, Mater Misericordiae Hospital, Dublin) Screening colonoscopy to splenic flexure (left sided colonoscopy) was offered to 738 asymptomatic volunteers ≥45 years in an area with high mortality rate for colorectal carcinoma. Five hundred were accepted and examined without premedication by an Olympus 100 cm colonscope after preparation by Fletchers enema. Splenic flexure was reached in 435 patients, descending colon in 49 with average duration of examination eight minutes. Examination failed in 16 patients. All polyps were biopsied and if adenomatous or ≥5 mm subsequent full colonoscopy/polypectomy was done. Of 180 patients with polyps, three had carcinoma, 86 adenoma, 45 hyperplastic and 35 had miscellaneous lesions. The adenoma group comprised 64 men (prevalence 20%) and 22 women (prevalence 12%). Thirty patients (35%) had more than one adenoma and 14 (16%) had adenomas >1 cm. Full colonoscopy in 94 patients showed adenomas proximal to splenic flexure in nine.

Our study shows that of 500 asymptomatic volunteers ≥45 years, 0.6% had malignant and 17-2% potentially malignant lesions in the left colon. The procedure, left sided colonoscopy, was acceptable (compliance 68%) and well tolerated.

Colonoscopic management of malignant polyps – an audit

I M CHESNER, S MULLER, M EGAN, J NEWMAN, AND E T SWARRICK (East Birmingham Hospital, Selly Oak Hospital, Birmingham and Newcross Hospital, Wolverhampton) Colon polypectomy is now accepted management for polyps, however, its role in the management of polyps with invasive malignancy is still subject to debate. One factor which may influence the outcome is the presence of vascular or lymphatic invasion.

We have examined the clinical and histological features in 70 malignant polyps removed at colonoscopy. Thirty six were judged to have carcinoma in situ, of which 35 had no further therapy. One had an anterior resection with no evidence of malignancy. There were no polyp related deaths during follow up (24–48 months). Of the 34 who had invasive carcinoma, 15 were judged to have had incomplete removal either endoscopically or histologically, all had surgery – seven had no evidence of tumour, all alive and well (12–55 months). Eight had tumour present: six Dukes’ A alive and well (24–48 months). One Dukes’ B, died 10 months and one Dukes’ C alive 36 months.

Nineteen were judged to have had complete excision and 17 had no further treatment. Thirteen alive and well (12–56 months) two had surgery. Both had residual tumour with evidence of vascular invasion. These results suggest that invasive carcinoma can be treated by polypectomy only if vascular invasion is excluded. If in doubt laparotomy is indicated.

Juvenile polyposis – a precancerous condition

J R JASS, C B WILLIAMS, B C MORSON, AND H J R BUSSEY (St Mark’s Hospital, City Road, London) Juvenile polyposis coli is inherited as an autosomal dominant condition and colorectal polyps number between 5–300. Patients usually present in the second decade with profuse rectal bleeding. Although the juvenile polypos is a hamartoma, associated colorectal malignancy has been described.

One thousand and twenty five polyps from 85 patients with juvenile polyposis have been examined. Eight hundred and thirty four were typical juvenile polyps; 70 (8%) showed mild and six (1%) showed moderate dysplasia. None showed severe dysplasia. One hundred and sixty eight were designated as atypical juvenile polyps. These were multilobated or papillary and comprised relatively more epithelium and less stroma than the typical variety. Fifty (30%) showed mild, 25 (15%) moderate and three (2%) severe dysplasia. The remaining polyps included 21 adenomas and two hyperplastic polypos. Sixteen patients had a colorectal cancer. Two cancers were confined to the head of a
Desmosomes and human colorectal cancer

J E MARSTON, D R GARROD, E P PARRISH, AND I TAYLOR (University Surgical Unit, Southampton General Hospital, Southampton) Reduced adhesion between malignant cells may result in some becoming dislodged, thus contributing to metastases. Desmosomes are adhesive intercellular junctions between epithelial cells. The presence and distribution of desmosomes in 47 primary colorectal cancers, eight peritoneal recurrences, and six liver metastases were studied using fluorescent staining with antidesmosomal antibody. Desmosomes were present in all tumours investigated, including metastases. In moderately well differentiated tumours the distribution was identical to uninvolved mucosa. The fluorescence was confined to opposing lateral membranes, being intense in the subapical regions and reduced towards the bases of the cells. In poorly differentiated tumours cell polarity was lost and desmosomal staining was evenly distributed around the cells. The desmosomal distribution in primary tumours and metastases was essentially similar.

The stability of desmosomal junctions to reduced extracellular calcium was also studied. In normal epithelium, junctions remained intact for at least 1-5 hours: between malignant cells, not only desmosomes but entire cell contacts were disrupted within 30 minutes and resulted in release of viable cell clumps. This differential adhesiveness of tumour cells in vitro may be of significance in understanding the development of colorectal metastases.

Immunohistochemical analysis of cell kinetic parameters in colonic adenocarcinomas, adenomas, and normal colons

P JOHNSTON, M O'BRIEN, P DERVAN, J CROWE, J LENNON, AND D N CARNEY (Departments of Gastroenterology, Pathology and Oncology, Mater Misericordiae Hospital, Dublin) The K1-67 antigen is a nuclear antigen expressed in the proliferative phases of the cell cycle (G1, G2, S and M). We used a monoclonal antibody to K1-67 and an immunohistochemical assay to study cell kinetics in fresh frozen sections of normal colon (12), colorectal carcinomas (30) and colonic adenomas (27). The K1-67 score represented the percentage epithelial cell nuclei which stained positively.

The K1-67 score ranged from 30 to 95 (mean 58) in carcinomas, 24-78 (mean 47) in adenomas, and one to 20 (mean 7-8) in normal colons. The K1-67 positivity in the normal colons was confined to the lower third to half of the crypt. By contrast adenomas showed positivity throughout including the surface epithelium. Widespread staining was also noted in carcinomas.

No correlation was noted between K1-67 score, histologic architecture and degree of dysplasia in adenomas and similarly no correlation was noted between the histologic grade or dukes staging in carcinomas.

The study of cell kinetics using K1-67 immunostaining in tissue sections provides new insights to the evolution of colonic adenomas and adenocarcinomas.

Photodynamic therapy (PDT) for colorectal cancer

H BARR, S G BOWN, AND N KRASNER (The Gastrointestinal Unit, Walton Hospital, Liverpool and The National Medical Laser Centre, Dept of Surgery, University College, London) Photodynamic therapy is a technique for local tissue destruction with light after prior drug sensitisation which has selectivity for malignant tumours. Animal experimental studies show that colorectal tumours necrose and slough whereas normal colon heals by regeneration without risk of perforation. We treated eight patients (four men, four women) aged 43-88 years with colorectal cancers, inoperable because of metastases (four), severe cardiac disease (three), or refusal of surgery (one). Five were below the perineal reflection (6-13 cm from anus) and three above (18-31 cm). Each was photosensitised with 2.5 mg/kg haematoporphyrin derivative (HpD) iv and treated two and eight days later with 630 nm red light from a dye laser, delivered via a 0.4 mm fibre passed through a colonoScope and inserted 1.5 mm into the tumour. Total energy at each site was 50 J. The depth of invasion, assessed by endosonography in six patients ranged from 0-7-3-2 cm. The mean depth of tumour removed at each treatment site was 0.54±0.28 cm (one week after treatment).

In four patients the total tumour volume was assessed before and after treatment, the volume removed was 5.1±2.2 cm (3-4 treatment sites each session). One tumour could not be detected endoscopically, endosonographically, or on biopsy after treatment (follow up five months). One patient with a large tumour required two units of blood two days after the second treatment. Photodynamic therapy is a promising method of treatment for small colorectal cancers.

Anal leukoplakia

D R DONALDSON, J R JASS, AND C V MANN (St Mark’s Hospital, City Road, London) Anal leukoplakia is a rare and ill understood condition. The clinical findings and pathology of 27 patients have been reviewed in order to assess the results of treatment and the association of the condition with anal cancer.

Patients presented with pruritus or an anal lump. Ages ranged from 31-79 (mean 60) years and the M:F ratio was 20:7. Examination revealed hard, granular white plaques surrounded by moist, thickened perianal skin. The lesion was either well circumscribed or circumferential. The histological findings were characterised by hyperkeratosis, acanthosis, ‘spiki’ downgrowth of rete ridges and a band-like chronic inflammatory cell infiltrate in the dermo-epidermal junction. There was a synchronous keratinising squamous cell carcinoma in nine patients (M:F=5:4, mean age 57 years) which was usually well differentiated. A tenth patient (female) developed a perianal squamous cell carcinoma 11 years after the diagnosis of leukoplakia – the patient having defaulted from follow up for four years. Patients with and without cancer were treated by surgical excision±skin flaps or grafts, but leukoplakia recurred in the majority of cases, often repeatedly. This study has shown that anal leukoplakia is frequently associated with squamous cell carcinoma and the condition recurs despite recourse to aggressive surgery. Patients need careful follow up and current surgical therapy requires re-evaluation.

Intraoperative pelvic cytology accurately predicts those at risk of developing local recurrence of colorectal cancer

CHRISTINE HALL, S H SILVERMAN, JANET MOORE, H THOMPSON, AND M R B KEIGHLEY (The General Hospital, Birmingham) Much

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polyp, one being a typical juvenile polyp showing mild dysplasia and the other a villous adenoma showing severe dysplasia. The mean age of patients with cancer was 34 years (range 15-59).

It is concluded that juvenile polyposis is a rare but important precancerous condition and that affected patients require careful surveillance and genetic counselling.
attention is currently being paid to the importance of lateral clearance during operation for colorectal cancer in order to prevent local pelvic recurrence. We have examined 50 patients using intraoperative cytology to detect residual pelvic disease and report the correlation between positive cytology and the incidence of local recurrence. The first 25 patients were examined by imprint cytology of tumour bed biopsies which were then submitted for histological examination. The second 25 patients were studied by scrape cytology of the four quadrants of the pelvis and histology was considered positive if there was tumour present in the perirectal fat. Eleven of the 50 patients had positive cytology. Two died in the immediate postoperative period; there were five local recurrences in the remainder at a median follow up of 20 months. Of the 39 negative patients, nine were considered positive on histological criteria, with one local recurrence. There were four local recurrences in the 30 patients negative on both criteria, a highly significant difference (0.5%>p>-0.25 2). We conclude that intraoperative cytology predicts those at risk of developing local pelvic recurrence. It is more important to detect malignant disease remaining in the patient than that removed with the histological specimen.

Fistulae in anorectal sepsis: the relevance of microbiology and necessity of repeat examination under anaesthesia

M C WINSLET, N S AMBROSE, AND A ALLAN (Selly Oak, General and Queen Elizabeth Hospitals, Birmingham) Isolation of colonic aerobes (CA) or ‘gut specific’ bacteriaeoides (GSB) from anorectal pus is reported to be indicative of a fistula, and in the absence of a demonstrable fistula is a specific indication for repeat examination under anaesthetic (EUA) to reduce recurrence. To confirm these proposals a retrospective review of 103 patients with cultured anorectal pus was performed: perianal abscess=65, ischiorectal abscess=38. Incision and drainage (I&D) was performed in 67 patients, and combined with EUA in only 36. A fistula was demonstrated perioperatively in seven patients (I&D=4, EUA=3) and in 11 at follow up (I&D=10, EUA=1), median three (1–36) months. CA/GBS were isolated in 71 patients (68-9%). Only 12 of 18 patients with a fistula had CA/GBS present. Of 59 patients (83%) with CA/GBS but no overt fistula only eight required further surgery, with 51 (71-8%) requiring no further treatment, median follow up two (2–4) years. Isolation of CA/GBS is suggestive but not diagnostic of a fistula. An initial EUA should be performed to exclude a fistula but irrespective of the culture a second EUA is not indicated as most patients remain asymptomatic. Occult fistulae are not responsible for the high incidence of recurrent sepsis.

Endoluminal ultrasound in benign anorectal disease

A DOBLE AND A J W SIM (St Mary’s Hospital, London) The role of endoluminal ultrasoundography in the management of rectal carcinoma is well established. This technique has not, however, been evaluated in benign ano rectal disease. Sixteen patients with a variety of benign anorectal diseases have been studied with the Bruel and Kjaer 1846 type ultrasound scanner. The sites of eight abscesses, three ischiorectal, three interspinchteric and two extrspinchteric, and a fistula-in-ano were correctly demonstrated. Three solitary rectal ulcers were shown to be mucosal lesions, as was a benign tubulovillous adenoma. Muscular defects were seen in one patient with a complete anal sphinteric division. In two patients with colorectal anastomotic defects and by study of in vitro sphinteric division in an abdomino-perineal resection specimen.

The results of this pilot study clearly show the capability of endoluminal ultrasonography in defining the pathological anatomy of benign anorectal conditions. Such definition will allow accurate diagnosis and permit a more rational treatment plan to be adopted.

Experience with small bowel endoscopy in Kuwait

BASIL AL-NAKIB, S RADHIKRISHNAN, LABIBA TAMIN, S M ALI, AND Y T OMER (Al-Amiri Teaching Hospital, Kuwait and Kuwait Cancer Control Centre, Kuwait) Endoscopic examination of the small bowel beyond the ligament of Treitz’s is done rarely, because of the relative infrequency of small bowel disease and lack of a suitable equipment. Over a two year period, we have done 180 such endoscopic examinations in 120 patients. A pediatric colonoscope (Olympus PCF) was used as a jejunoscopy by the push type method, and the jejunum up to 60 cm from the duodeno jejunal flexure was examined with target biopsies. Abnormalities were present in 81 (69%) patients. In the 19 patients who had immunoproliferative small intestinal disease (IPSID), four endoscopic groups could be
described. Among the 17 patients who had subtotal villous atrophy, the mucosa looked almost normal endoscopically in the children, while oedema, diffuse nodularity and ulcerations as seen in IPSID was observed in three adults. A large jejunal polyp was found to be the source of an obscure gastrointestinal bleeding. In addition, six patients who had duodenoenjunal Crohn’s disease, two with schistosomal jejunitis, and one with Hencoh-Schonlein purpura were diagnosed by jejunoscopy and histology. Thus direct examination of the mucosa with biopsies was of significant value in our region, where a variety of small bowel pathology exist.

**Paediatric upper G1 endoscopy – an experience of 531 cases**

P K H Tam (introduced by Professor R Shields) (Division of Paediatric Surgery, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong; present address: Department of Child Health, Alder Hey Children’s Hospital, Eaton Road, Liverpool) Reports on the use of flexible G1 endoscopy in the paediatric population have been scarce. Our experience of 531 examinations on 364 children (age range 1 month–16 years) in the past 12 years represents one of the largest series available and illustrates the advantages of having such a service in a regional centre.

The vast majority of our procedures did not require anaesthesia. Indications included upper G1 bleeding (99), abdominal pain (168), foreign body ingestion (76), vomiting (10), dysphagia (5), reasessment (149), miscellaneous (24). Findings were chronic peptic ulcer (47), gastroduodenitis (59), neoplasm (5), foreign body impaction (19), varices (7), scirrhosis (4), normal (201), recurrent disease (32), healing pathology (114), miscellaneous (59). GI bleeding had the highest diagnostic yield (84.8%). Routine endoscopic assessment of response to ulcer therapy was valuable in detecting recurrence (27.4%) and guiding treatment. The only pitfall associated with flexible endoscopy was the failure of detection of recurrent tracheo-oesophageal fistulas in two infants. In this age group, the available endoscopes are still not optimal for this purpose. ERCP was successfully performed in 11 children with biliary and pancreatic problems and gave useful anatomical information to guide management.

Therapeutic procedures (55) included injection sclertherapy (32), foreign body removal (19), and endoscopic-guided bouginage of oesophageal stricture (four). Results were uniformly satisfactory. In particular, we have found that stricture management was markedly improved by the use of the new technique of balloon dilatation. We had no morbidity.

**Gastric vascular ectasia: nine cases and treatment by laser photocoagulation**

J E Coxon and D E Beckly (Plymouth General Hospital, Plymouth, Devon) Gastric vascular ectasia (watermelon stomach) is a cause of chronic severe upper gastrointestinal blood loss. The condition is rare with only 17 previously recorded cases. We present nine further cases and suggest:

1. The condition may be more common than supposed. In four of our cases the typical appearances were described at a previous endoscopy but the condition was not recognised by the endoscopist.
2. There may be an association with pernicious anaemia. Three of our cases were receiving B12. The median B12 of the other cases was 202 (range 163–256).

All but one of the patients had a micrrocystic anaemia at the time of diagnosis but of five patients who had a previous unrelated admission, four had an MCV greater than 95. One patient had antiparcellar cell antibodies. (3) The treatment of choice is a distal gastrectomy, performed successfully in two of our patients. Four patients refused or were not fit for surgery and in three of these patients the condition was treated by laser photocoagulation of the affected portion of the stomach using a NdYAG laser. Blood loss measured with Cr51 labelled red cells in ml/day was significantly reduced by photocoagulation (before 140, 80, 72.5; after 0-4, 0-56, 1-85).

**CO2 v air – an evaluation of discomfort after colonoscopy**

J A Wilson, E J Irvine, R Goodacre, J O’Connor, and G Stevenson (Divisions of Gastroenterology and Radiology, McMaster University, Hamilton, Ontario, Canada) Much of the discomfort after colonoscopy is caused by air insufflated endoscopically. Carbon dioxide (CO2) is absorbed more rapidly than air from the colon and may cause less pain. Fifty six patients undergoing colonoscopy were randomised in double blind fashion to insufflation with air or CO2. Symptoms were evaluated by questionnaire at one, six, and 24 hours after colonoscopy. Abdominal radiographs taken one hour after colonoscopy were scored for gaseous distension and operator questionnaire evaluated adequacy of procedure and technical difficulty.

During colonoscopy mean pain score of 1.7 for air and 1.8 for CO2 were similar. At six and 24 hours, gas passed with air was greater (p<0.001). At six hours pain score was 0 and 0.8 (p<0.001) and at 24 hours was 0 and 0.7 (p<0.001) for CO2 and air respectively. Forty five radiographs were evaluated in five categories – 16 of 17 with CO2 in the first three (no gas to slight excess) and 28 of 28 (p<0.001) with air in the last two (moderate to severe excess). There was no difference in operator evaluation for air or CO2.

Insufflation with CO2 causes less pain to patients and no extra difficulty to endoscopists. We recommend its routine use in colonoscopy.

**A study of intracolic hydrogen and methane concentrations in patients**

J Crowe, J Lennon, and E A Gallagher (Gastrointestinal Unit, Mater Misericordiae Hospital, Dublin, Ireland) Samples of intracolic gas were obtained during routine colonoscopy from three groups of patients – namely, polyethylene glycol (PEG) (n = 23), samples = 38), phosphate enema (n=34, samples=41) and mannitol (n=4, samples = 8). Chromatograph analysis was done on each sample for nitrogen, oxygen, methane, hydrogen, carbon dioxide and water. Air insufflation was used during each procedure. In the PEG group, potentially explosive concentrations occurred in six of 38 samples, 1–10% relative concentration. In the phosphate enema group, four of 41 gas samples had 1–10% relative concentration and in the mannitol group two of eight samples. No sample had potentially explosive concentrations of methane. All preparations were judged to be good by the endoscopist. All patients had a coexisting oxygen concentration of 5% or more, necessary for combustion of hydrogen or methane in their explosive ranges.

These results show that pockets of gas containing potentially explosive concentrations of hydrogen may occur in the colon after preparation with PEG, mannitol or phosphate enema, and that carbon dioxide (an inert gas) insufflation should always be used if diathermy is to be used.

**Radial pressures during stricture dilatation with bougies and balloons**
It has been suggested that balloon dilatation of oesophageal strictures may be gentler than bougienage, and that less force is needed. To assess this pressure recordings were done during bougie dilatation in eight patients with benign oesophageal strictures (mean stricture diameter 7-25 mm). Initial dilatation was carried out with Celestin dilators. The dilatation was completed with a size 58 Fr Eder-Puestow bougie specially modified with a side hole catheter implanted at its waist, connected to a pressure transducer; pressure recordings were made throughout the dilatation. The pressures measured were the final dilating pressures for each dilatation. The results showed that in five out of eight patients this pressure exceeded 49 kPa (370 mm Hg) and in the three others patients was an average of 31 kPa (230 mm Hg).

In 45 strictures (mean diameter 7-6 mm) dilated by a 20 mm balloon, the final dilating pressure was up to 151 kPa (1133 mm Hg) in 39 patients and between 151 and 302 kPa (2266 mm Hg) in six patients. Dilatation was incomplete in one patient in each group.

Very high pressures are used in both forms of stricture dilatation. Balloon dilatation may be inherently safer and more effective as these pressures are applied only in a radial direction, but this awaits confirmation.

Endoscopic sphincterotomy for common bile duct calculi in patients with gall bladder in situ considered unfit for surgery

B R DAVIDSON, J P NEOPOTLEOMOS, AND D L CARR-LOCKE (Departments of Surgery and Gastroenterology, University of Leicester, Leicester) Endoscopic sphincterotomy (ES) was attempted in 106 patients with common bile duct (CBD) calculi and gall bladders present who were considered unfit for surgery on the grounds of age and frailty alone (35%) and/or the presence of major medical problems (65%). Endoscopic sphincterotomy was successful in 105 cases (99%). Early ES related complications occurred in 21 patients (19-8%). There were 12 hospital deaths (11-3%) of which five were due to biliary causes (4-7%). Complications were more frequent in patients in whom initial ES did not clear the CBD (p<0-02) and mortality was greater in those without confirmation of CBD clearance (p<0-01) unless operated upon. Twelve patients developed gall bladder complications (11-3%) including five with empyema (4-7%). Analysis of clinical, haematological and biochemical factors together with ERCP findings revealed pre-existing cholangitis to be the only factor of any value in predicting gall bladder complications.

These results suggest that an active policy of CBD stone clearance should be followed and that clearing should be confirmed as far as possible. Mortality from post-ES complications might be further reduced by use of other non-operative interventional techniques.

Endoscopic management of large (>2 cm) CBD stone associated with recurrent pyogenic cholangitis

J W C LEUNG, S C SCHUNG, S D MOK, AND A K C LUI (Combined Endoscopy Unit, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong) The technical difficulty and risk involved with endoscopic stone extraction increases with size of the common duct stone. Stones >2 cm are traditionally referred for surgery. Patients with recurrent pyogenic cholangitis often have large, muddy, calcium bilirubinate stones as the cause of biliary obstruction. From January 1985 to November 1986, we had 32 patients (M=12, F=20; age 36-85 years, mean=69 years), with CBD stones greater than 2 cm (greatest diameter 2-0-3-6, mean=2-8 cm). The mean diameter of the distal CBD was 1-06 cm; 47% had significant cardiorespiratory problems. Seventeen (53%) had acute supplicative cholangitis requiring emergency drainage with a nasobiliary catheter. Stone extraction was attempted with large (6 cm) baskets and mechanical lithotripsy after sphincterotomy. Chemical dissolution was performed with 1% EDTA solution infused via the nasobiliary catheter.

Sixteen (50%) had duct clearance after a mean of 2-8 sessions (range 1-5) with no mortality. The main reason for failed duct clearance was the lack of space within the CBD to open the basket. Sixteen with failed duct clearance underwent surgery (exploration of CBD alone, choledochoduodenostomy 15) with two deaths.

We conclude that a combined use of large baskets and chemical dissolution with 1% EDTA and if necessary, mechanical lithotripsy can remove CBD stones of >2 cm with safety.

Endoscopic prosthesis for common bile duct stones

I M DIAS, S R CAIRNS, P R SALMON, AND P B COTTON (Department of gastroenterology, The Middlesex Hospital, London) During a three year period to February 1987, 624 patients underwent successful endoscopic sphincterotomy for common bile duct (CBD) stones. Ninety of these patients had incomplete duct clearance at the first attempt, principally because of the stone size, and had one or more endoscopic prosthesis (EP) inserted into the CBD. There were two procedure related deaths, one limited post sphincterotomy haemorrhage and one failed stent insertion.

Follow up of 31 patients (mean age 71-1 years) given EP as a temporary measure was up to 3-1 months (mean 2-5). All patients subsequently had complete duct clearance.

19 endoscopic and 12 at laparotomy. There were no deaths. Twenty five patients (mean age 83-8 years) considered unsuitable for further endoscopic or surgical therapy were given EP as definitive treatment and followed-up to 37-9 months (mean 18-1). During follow up three patients have died from non-biliary diseases, and only two have required endoscopic stent changes for cholangitis. There were no biliary related deaths.

These results suggest that when stones can not be removed endoscopically: (1) temporary stenting permits further elective endoscopic or surgical therapy; (2) long-term stent placement may provide a useful therapy for poor risk surgical candidates.

Open access colonoscopy: a single investigation for suspected colonic neoplasia

J J T TATE AND G T ROYLE (INTRODUCED BY I TAYLOR (University Surgical Unit, Royal South Hampshire Hospital, Southampton) It has been suggested that colonoscopy should be the primary investigation of occult or overt colonic bleeding. We report the results of providing an open-access colonoscopy service to general practitioners for such patients.

All general practitioners in one health district were advised of the service by letter. Patients were sent an appointment to attend for colonoscopy without prior hospital interview, sigmoidoscopy or barium enema. In a 12 month period 136 referrals were received from 53 general practitioners.

Colonoscopy was performed on 131 patients (age 19-83, median 63 years). Six patients did not attend and colonoscopy was contraindicated in one. The entire colon was examined in 92% and there were no complications. Findings were carcinoma in...
12 patients (Dukes' stage A=4, B=3, C=5); adenomatous polyps in 22; diverticulardisease in 35; colitis in 9 and no abnormality in 53.

We conclude that open access colonoscopy has provided a rapid, safe and complete examination of the large bowel with a high detection rate for neoplasia (26%) and has combined treatment (polypectomy) with diagnosis in two thirds of these cases.

Open access fibrecolonscopy: a comparative audit of efficacy

I KALRA, W R PRICE, B J M JONES, AND A N HAMLYN (Department of Gastroenterology, Russells Hall and Wordsley Hospital, Dudley Health District, Dudley) We studied 541 open access referrals and compared them to 495 hospital initiated fibresigmoidoscopies over five years. Though the number of open access fibresigmoidoscopies doubled over this period, diagnostic yield remained unchanged at 40% and was similar to the yield in hospital initiated procedures. Colorectal carcinoma was seen in 64 open access compared to 47 hospital referred patients, the proportion of Dukes' A lesion being similar in both groups (34%). Carcinoma was not seen in patients under 40 years of age. Fibresigmoidoscopy was unsatisfactory in 54 (open access 31, hospital 23) and pathology was missed in 12 (open access seven, hospital five) patients. There were no significant operator differences.

High diagnostic yields were associated with diarrhoea and rectal bleeding (90%), altered blood per rectum (95%) and rectal bleeding associated with pain (100%). Low yields were associated with abdominal pain as sole cause of referral (0%), constipation (9-3%) or abdominal pain with constipation (8-2%). Diagnostic rate was significantly low in open access patients under 40 years of age (19-2%).

Referral was considered justified in 475 (87-8%) patients and only 54 (16-6%) patients with a normal endoscopy required further investigations.

We conclude that open access fibresigmoidoscopy is effective and cost efficient. Appropriate patient selection on basis of age and symptoms can reduce referrals by 38% and improve diagnostic yield by 25% without affecting sensitivity.

FUNCTIONAL BOWEL

Fructose and sorbitol malabsorption in patients with functional bowel disease

J J RUMESSEN AND E GUENAND-HOYER (INTRODUCED BY P M CHRISTIANSEN (Dept of Surgical Gastroenterology, Hvidovre University Hospital, Denmark and Department of Gastroenterology and Internal Medicine F, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark) The absorption capacities and the symptom production of fructose, sorbitol, fructose-sorbitol mixtures and sucrose was investigated by means of hydrogen breath tests in 25 consecutive patients with functional bowel disease. A 25 g dose of fructose was malabsorbed by 13 patients, in seven of these the absorption capacity was below 15 g. In contrast, malabsorption of sucrose was never seen. Fructose malabsorption caused significantly increased abdominal distress compared with the group of patients with complete absorption of fructose or compared with ingestion of sucrose. A 5g dose of sorbitol was malabsorbed by eight of the fructose malabsorbers. Mixtures of 25 g fructose and 5 g sorbitol caused significantly increased malabsorption and abdominal distress, and in eight of the fructose malabsorbers the effect on malabsorption was more than additive.

These results show that malabsorption of small amounts of fructose, sorbitol and mixtures thereof is significant and symptom provoking in patients with functional bowel disease. The findings may have direct implications for the dietary guidance to a major group of patients with functional bowel disease and raise the possibility of defining separate entities in this disease complex.

Current spectrum of intestinal obstruction

G P MCENTEE, D PENDER, D MULVIN, M MCCULLOUGH, S NAEDER, S PARAI, M S BADURDEEN, V FERRARO, C CHAM, N GILLHAM, AND P MATTHEWS (North Tees General, Darlington Memorial, Bishop Auckland General, Hartlepool General Hospitals) This prospective study was set up to accurately determine the current spectrum of intestinal obstruction in the UK. During a 12 month period (1 Aug '85–1 July '86) 228 patients required a total of 236 admissions to one of four neighbouring district general hospitals serving a total population of 591 000 – an overall incidence of 39-9 cases per 100 000 per annum. Aetiological factors included adhesions (75 (32%)), intraperitoneal malignancy (26 (32%)), and mesenteric adhesions (25 (5%)).

The peak incidence of obstruction due to adhesions, hernias and intra-abdominal malignancies each occurred in the eighth decade of life. Urgent surgery (within 48 hours of admission) was performed in 30% of all adhesions (22%), 61% hernias (40), and 30% of intra-abdominal malignancies (18). Overall mortality was 11-4% (26 deaths) and post-operative mortality was 12-3% (19 deaths).

Twenty two patients required a total of 2993 inpatient hospital days as a result of intestinal obstruction. Strangulated hernias and large bowel malignancy still account for over 50% of all cases of intestinal obstruction in the UK today. A more aggressive approach aimed at earlier detection and elective treatment of both conditions should be balanced against the risk of postoperative morbidity + mortality in what is predominantly an elderly age group.

Studies on the genesis of colic

M A STOKES, K J MORIARTY, AND B N CATCHPOLE (Departments of Surgery and Medicine, Universities of Manchester and Western Australia, Hope Hospital, Salford) ‘Colic’ is a clinical term which has defined a precise definition. We have examined those motor events in the gut associated with simulated ‘colic’. Two 5-lumen tube systems, each carrying a balloon, were used. One lumen inflated the balloon while two sensed pressure proximally and two distally to it by suitable ports, which thus assessed contractions over 24 or 32 cm of gut. Sensing channels were water perfused (0.2 ml/min) and recorded via transducers on a rectilinear polygraph. ‘Colic’ was induced by balloon inflation followed by saline bolus injection via the port immediately orad to it. Studies were made of the duodenum, jejunum, ileum and colon passing the tube system orally, via stomas or per rectum.

(1) Pain was invariably associated with a rise of baseline pressure, indicating contraction in a gut segment, at least 6 cm and sometimes 32 cm long. (2) With pain, baseline pressures varied widely between patients. (3) Solitary painless contractions of waves of >250 mm Hg occurred. (4) Duration of pain was similar in both small (44±13 sec, mean±SD) and large (38±17 sec, mean±SD) intestine. (5) Location of pain, referable to gut segments, was variable and increasing severity, pain spread across.
Do patients with disordered defecation have a primary personality disorder?

S E FISHER, M R B KEIGHLEY, K BRECON, V SMART, AND H ANDREWS (Department of Surgery, The General Hospital, Birmingham) It is uncertain whether patients with disordered defecation have a personality disorder. We investigated patients with chronic constipation (n=21) and faecal incontinence (n=29) who were offered surgical treatment. Patients were subdivided into those whose symptoms were controlled by surgery and those who were not improved. Patients were investigated using the HAD scale and the General Health Questionnaire. Their psychological state was assessed preoperatively and six to 12 months postoperatively and the results compared with a group of age/sex matched controls (n=50). Statistical analyses were performed using the Mann Whitney U two tailed test. Constipated patients had significantly higher HAD depression scores compared with controls (6 (2-12) v 4 (0-8), p<0-05). Patients who were improved (n=13) by operation could be identified preoperatively by significantly lower HAD anxiety scales compared with those who were not improved (n=8), 8 (3-14) v 15 (10-19), p<0-02) and by significantly lower HAD depression scores (4 (2-12) v 7 (5-11), p<0-01). Operation itself, however, had no influence on psychological scoring. Incontinent patients did not differ from the controls using the parameters tested and the group improved by operation (n=14) could not be identified preoperatively.

These data indicate that only constipated patients have a personality disorder and that those likely to be improved by operation can be identified beforehand.

Diagnosis of allied functional bowel disorders using monoclonal antibodies and electronmicroscopy

P PURI, T FUJIMOTO, AND BRIAN LAKE (C FEIGHLEY) (The Children’s Research Centre, Our Lady’s Hosp for Sick Children, Crumlin, Dublin 12 and The Hosp for Sick Children, Great Ormond Street, London) There are a number of conditions which clinically resemble Hirschsprung’s disease despite the presence of ganglion cells on rectal biopsy. These conditions have been classified on the basis of symptoms under various names such as pseudo Hirschsprung’s disease, chronic adynamic ileus and chronic idiopathic intestinal pseudo-obstruction. There have been no systemic studies to date to distinguish these conditions from one another. We examined biopsy and surgical specimens from 19 cases of allied functional bowel disorder by enzyme histochemistry (AChE), silver impregnation and electron microscopy in an attempt to establish the most appropriate diagnostic procedure. A monoclonal antibody D23 produced in our own laboratory is a good marker of the autonomic nervous system. This unique antibody distinguishes various neuronal abnormalities of the bowel except abnormalities of the argyrophil plexus which are diagnosed by silver staining.

Six of the 19 cases had a smooth muscle disorder – for example, visceral myopathy, inclusion bodies etc. which could only be diagnosed on electron microscopy. Our data suggest that the vast majority of allied functional bowel disorders can be diagnosed by examining a full thickness rectal biopsy by immunocytochemistry, silver impregnation and electron microscopy.

Effect of indomethacin and ranitidine on gastric acidity

R P WALT, P PRICHARD, T DANESHMEND, N SMITH, AND M LANGMAN (Department of Therapeutics, University Hospital, Nottingham) The non-steroidal anti-inflammatory agents have been implicated in the pathogenesis and complications of peptic ulcer. It is unclear which mechanisms are involved, but increased acid secretion could be one. Indomethacin enhances histaminergic and basal but not food stimulated acid secretion. Prolonged unbuffered acidity is also an important factor in peptic ulcer treatment. We have therefore investigated the effects of indomethacin and ranitidine on nocturnal gastric acidity in 10 normal volunteers. Each underwent four randomised studies after seven days treatment with indomethacin (50 mg tds) and/or ranitidine (300 mg at 1900 h), or placebo (double-dummy). Acidity was measured on half hourly aspirates of gastric contents from 1900 h to 0800 h. Environmental conditions including meals were identical on each study day. Median acidity (range) during the night (2200 h–0800 h) was 41-7 mmol/l (67-6–25-1) on pla/pla; 39-8 (63-1–24-0) on ind/ pla; 0-36 (21-3–0-0) on pla/ran; 0-77 (43-7–0-0) on ind/ran. Ranitidine significantly decreased acidity irrespective of concomitant indomethacin treatment (p<0-01, Wilcoxon) and indomethacin alone did not significantly affect acidity. This suggests that ulcerogenic effects of indomethacin are not due to increased acidity and that ranitidine should be effective therapy even in patients receiving indomethacin.

Isolated duodenal tamponade in the treatment of bleeding duodenal ulcer

T V TAYLOR AND A L BLOWER (Department of Surgical Gastroenterology, Manchester Royal Infirmary, Oxford Road, Man-
Is highly selective vagotomy (HSV) a good operation for duodenal ulcer (DU)? A longer look at the answer

K S DUA, M KORUTH, P W BRUNT, AND N A MATHESON (Departments of Surgery and Gastroenterology, Aberdeen Royal Infirmary, Aberdeen) Highly selective vagotomy is now well recognised as a treatment for DU although the long term efficacy is less well established. We have previously reported the early results (at a mean of five years postoperatively) of 137 patients operated on by one surgeon and randomly allocated to either HSV or truncal vagotomy and pyloroplasty (TVP). Highly selective vagotomy was significantly superior in Visick grading (p=0.05) and side-effects – for example, diarrhoea, p=0.001.

We have resurveyed the same patients at a mean of 11 (minimum eight years post-operatively. There is no difference on blind assessment using rigorous Visick grading between HSV and TVP (Grades I+II, 75.4% and 74.5% respectively). Nearly one-fifth (18.6%) of TVP patients (but none of the HSV patients) had required re-operation in the intervening period, however – either hemigastrectomy or pyloric reconstruction. The endoscopic proven recurrence rate for HSV was 5%.

Although HSV is a technically more demanding procedure we regard it as a clearly superior operation to TVP in almost all respects and longterm follow up supports this optimism.

Nd-YAG laser therapy in patients with gastric and duodenal malignancies – an initial experience

J R ANDERSON AND C G MURRAN (University Department of Surgery, Royal Infirmary, Glasgow) Thirty patients (24 men and 6 women) of mean age 67 year (range 48–84) with gastroduodenal malignancies were referred for laser therapy. The reason for referral was inoperability (n=14) unfit for laparotomy (n=7), widespread metastases (n=7) and refused surgery (n=2). The tumour sites were fundus in 12 (involving cardio in 10), body in four, proximal two thirds in two, distal two thirds in five, antrum in three, total stomach in three, and 2nd part duodenum in one. The major symptoms for which relief was sought were bleeding in 21, dysphagia in 11, and vomiting from gastric outlet obstruction in eight. On average two laser sessions (range 1–7) were given to each patient.

Relief of symptoms was achieved in 19 of the 21 patients with bleeding, 10 of the 11 patients with dysphagia with recurrence of symptoms needing Celestin intubation in four, and in five of the eight patients with gastric outlet obstruction. Partial relief of outlet obstruction was obtained in two patients who were able to manage fluids only. Seventeen of these patients have, to date, died with a mean survival of nine weeks. The mean survival of the remaining 13 patients is 28 weeks (range 3–76 weeks).

Palliative laser therapy offers relief of symptoms to a significant number of patients with gastroduodenal malignancies unsuitable for surgery, in whom therapeutic options are otherwise limited.

Smoking affects mucosal gastrin and gastric acid secretion in duodenal ulcer (DU)

W M HUI, M CHAN, AND S K LAM (Departments of Medicine and Clinical Biochemistry, University of Hong Kong, Queen Mary Hospital, Hong Kong) Smoking adversely affect the healing of DU and smokers have a higher maximal acid output (MAO) but the pathophysiological basis is not known. To investigate this, 30 patients (male, 95% age: 35.23±1.79; smokers 33.3%) with active DU, documented endoscopically were recruited for the study. The MAO, the parietal cell sensitivity to gastrin (D2oC), fasting and meal-stimulated gastrin responses were measured. During endoscopy, three biopsies were taken from the body of the stomach for the estimation of histamine and 2 from the antrum for the estimation of mucosal gastrin. Seven non-ulcer subjects (age 42.7±7.0, male 43%, 28.6% smoker) were recruited as controls. The results (expressed in mean±SE) showed that MAO was significantly higher in the smokers (32.3±3.5 nmol/h) than the non-smokers (24.8±1.9) (p<0.05). The mucosal gastrin content was significantly higher in the smokers (74.2±16.2 fmoles/mg) than non-smokers (41.7±5.9) (p<0.05) and both were higher than the controls (15.4±5.7) (p<0.01). In both smokers and non-smokers the mucosal histamine (28.3±4.4, 28.8±5.1 ng/ml), fasting gastrin level (5.1±0.5, 5.3±0.8 nmol/l), meal stimulated gastrin response (1.5±0.1, 1.6±0.29, 5.1±0.5; 0 min/min) and D2oC (144.6±3.1, 196.3±66.3 ng/kg/h) were similar. We concluded that the increased MAO in smokers is associated with increased antral gastrin, suggesting that the latter is important in the pathogenesis.

Basal and stimulated plasma gastrin in duodenal ulceration (DU): correlation with failure of H2 receptor antagonists (H2RA) and with recurrent ulceration (RU) after highly selective vagotomy (HSV)

K S NAIK, M LOGOPoulos, J N PRIMROSE, R L BLACKETT, AND D JOHNSTON (University Department of Surgery and Anatomy, The University, Leeds and Leeds General Infirmary, Leeds) The aim was to determine the influence of gastrin and the proposed ‘g-cell hyperfunction’ in H2RA resistance and recurrence after HSV in 71 DU patients. Basal (BG) and integrated gastrin responses to meal (IGRM) and insulin (IGRI) were measured before and after HSV for DU, BAO, PAO (Pentagastrin) and PAO (Insulin I) were measured pre- and post-operatively. The pre-operative response to H2RA was recorded. Patients were followed up for five years to detect RU. There was no difference between BG, IGRM and IGRI in H2RA resistant and non-resistant RU and non-RU patients. There was a positive correlation between preoperative IGRM and postoperative BAO (p=0.02). Inte-
grated gastrin responses to meal correlated inversely with percentage reduction in BAO postoperatively (p=0.02). An inverse correlation was observed between both preoperative and postoperative IGRM and PAO(I) (p=0.03). A positive correlation was shown between postoperative IGRM and postoperative PAO(I) (p=0.03).

G-cell hyperfunction is not an important cause of resistance of H2-RA or of RU after HSV. Correlations between preoperative IGRM and postoperative BAO and percentage reduction in BAO have been demonstrated. Some of the acid response to insulin after HSV appears to be mediated by gastrin.

Recurrence of duodenal ulcers during maintenance treatment

J PENSTON, D CARTER, AND K G WORMSLEY (Ninewells Hospital, Dundee) The clinical course of 413 patients with endoscopically healed duodenal ulcer has been studied. Thirty seven of the 339 patients (11%) receiving maintenance treatment with an H2 receptor antagonist suffered their first relapse during the first year; 44/268 (16%) during the second year; 21/168 (13%) during the third year; 11/105 (10%) during the fourth year and 3/51 (6%) during the fifth year. Sixty three per cent of first relapses were asymptomatic. After endoscopically confirmed re healing of the first relapse, 50 patients again received maintenance treatment with 150 mg ranitidin at night while 46 patients received maintenance treatment with the increased dose of 300 mg at night. During the first year after relapsing, 3/46 (4%) patients receiving 150 mg ranitidine at night relapsed, compared with 0/43 receiving 300 mg ranitidine. The subsequent relapse rates were 1/26 (4%) and 1/34 (3%) during the second year of further maintenance treatment and 2/17 (12%) or 1/17 (6%) during the third year, respectively.

We conclude that maintenance treatment is effective in sustaining remission of the majority of patients with duodenal ulcer. The relapse rate during maintenance treatment decreased significantly during the course of time. Patients who developed recurrence during maintenance treatment seemed more likely to remain in remission if a higher dose of gastric secretory inhibitor was used for treatment.

Prospective randomised controlled trial of conservative therapy versus surgery for perforated duodenal ulcer

T J CROFTS, R J C STEELE, S C S CHUNG, K PARK, AND A K C LI (Department of Surgery, The Chinese University of Hong Kong, Hong Kong) With the establishment of H2 receptor blockers in the treatment for duodenal ulcer combined with the use of effective antibiotics, we studied if surgical intervention is always indicated for patients with perforated duodenal ulcer disease.

Eighty four consecutive patients with definite diagnosis of perforated duodenal ulcer were randomly allocated to one of two treatment groups, surgery or non-operative (antibiotics, nasogastric suction and H2 receptor blockers) treatment. The types of surgery performed depended on the patient fitness and the surgeons’ experience. All conservatively treated patients were managed by one team and constantly assessed. If there was no improvement by 12 hours after admission, they were referred for surgery and deemed a failure of conservative therapy.

There was one trial exclusion leaving 83 patients for analysis; 40 in the conservative group and 43 in the surgery group. Both groups were comparable for age, sex, ulcerogenic factors and presence of coexistent disease.

Ten patients (25%) failed on conservative therapy but 75% of patients did not need surgery.

Overall mortality was 4-8% and equal in both groups. Comparison of morbidity between conservative therapy versus surgery as measured by abscess formation (6 v 2), hospital stay (12 days v 8-8 days) and duration of antibiotic treatment (7-8 days v 5-7 days) all favoured the surgery group. However a subgroup was identified in which conservative management may be indicated in preference to surgery.

Omeprazole or ranitidine in the treatment of reflux oesophagitis – result from a double blind, randomised, Scandinavian multicentre study

I LUNDELL, O FAUSA, AND S SANDMARK (introduced by a Walan) (Dept of Surgery II, Sahlgrenska Sjukhuset, Göteborg, Dept of Medicine A, Rigshospitalet, Oslo, and Dept of Otorhinolaryngology, Regionsjukhuset, Örebro, Norway) One hundred and fifty two patients with erosive and/or ulcerative oesophagitis were randomised to treatment with omeprazole 20 mg, once daily or ranitidine 150 mg bid. Endoscopy was done immediately before entry and after four and eight weeks’ treatment together with assessment of symptoms. Macroscopic healing of oesophagitis was defined as complete epithelialisation of all oesophageal lesions. One hundred and forty four patients completed the first four weeks of treatment according to the protocol and the healing rates were 67% for omeprazole and 31% for ranitidine (p=0.0001). The same great differences in healing rates were seen also after eight weeks treatment; 85% and 50% for omeprazole and ranitidine, respectively (p<0.0001).

The British Society of Gastroenterology

OESOPHAGUS

Value of omeprazole in the management of erosive oesophagitis refractory to high dose cimetidine

K D BARDHAN, PAMELA MORRIS, MARY THOMPSON, D S DHANDE, R F C HINCHLIFE, M J DAILY, N J H CARROLL, AND CATHERINE KRAKOWCZYK (District General Hospital, Rotherham and Astra Clinical Research Unit, Edinburgh) Refractory erosive oesophagitis (REO) is defined as persistence of ulceration or erosion despite treatment with cimetidine (CIM) 3-2 g daily for ≥3 months. To assess if greater acid suppression might prove more effective in medical management, 38 patients with REO were treated with omeprazole (OME) 40 mg daily for up to eight weeks. Endoscopy, clinical assessment and laboratory studies were done at the start, at four weeks and at eight weeks (if unhealed earlier). Oesophagitis was graded 0–4. The demographic features were: mean age 61 years; males 50%; smokers 32%; regular NSAID users 11%; obese 47%; mean duration of symptoms 9-9 years. Cimetidine treatment, before OME therapy, was on average: at 1-6 g daily; 18 months; at 2 g, 16 months; at 3-2 g, five months (total 39 months). Endoscopic appearances improved in 28 patients after four weeks’ treatment and in a further seven by eight weeks. The cumulative changes at eight weeks were: healed 42%; almost completely healed 45%; unchanged 13%. Symptoms were completely relieved in 58%, improved in 32%, unchanged in 8%. Adverse events were infrequent and did not require discontinuing OME. There were no clinically significant changes in haematology or in biochemistry. Of 28 patients returned to maintenance CIM, 50% were in remission after 1–19 months. In conclusion, omeprazole heals or improves oesophagitis and relieves symptoms when refractory to high dose cimetidine.
Omeprazole gave also a faster and more substantial improvement in reflux symptoms. In the overall evaluation of symptoms, treatment with omeprazole was superior to ranitidine already after one week and throughout the study. Heartburn resolved completely in 77% of patients receiving omeprazole during the first four weeks compared to 36% in those receiving ranitidine (p<0.0001). There were no adverse events or clinically significant changes in the laboratory screen attributable to the trial medications. The present study has shown that omeprazole 20 mg once daily, is superior to ranitidine both in promoting healing and relieving symptoms in patients with erosive and/or ulcerative oesophagitis.

Cisapride and gastrooesophageal reflux in children with or without neurological disorders

G S Clarke, B Sandhu, N Gilbertson, and M J Brueton (Dept of Child Health, Westminster Children’s Hospital, London)

Cisapride was used to treat 22 children who had significant gastrooesophageal reflux demonstrated by 24 hour pH monitoring. Fifteen of these children were neurologically normal (Gp I), seven had major central nervous system abnormalities (Gp II). All the patients underwent repeat pH monitoring after three weeks treatment with cisapride. The results were compared using the Wilcoxon test. After cisapride treatment Gp I showed a significant decrease in median % time pH <4 (19.2-9.5; p<0.01); longest reflux time (36.5-17.2 mins; p<0.02); and average reflux duration (7.1-2.1 mins; p<0.01) indicating a significant increase in oesophageal clearance rate.

In Gp II the only significant change was a decrease in % time pH >7 (1.8-0.0; p<0.01). In general this group was relatively unresponsive to treatment with cisapride. Ranking the responses to treatment of both groups showed a high probability that the two groups were responding differently (p>0.05, Spearman Ranking test).

Cisapride whose gastrokinetic properties are mediated peripherally is effective in treating children with gastrooesophageal reflux who do not have central nervous system abnormalities.

Comparison of Asilone gel and Gaviscon liquid in the treatment of reflux oesophagitis

H L Smart and M Michael Atkinson (Department of Surgery, University Hospital, Nottingham) Antacid and alginate or dimethicone combinations are perhaps superior to simple antacids in treating oesophagitis. As there is a lack of data on these combinations we have performed a study comparing two commonly prescribed preparations. Fifty three patients with symptomatic, endoscopically proven oesophagitis were randomly allocated to receive Asilone gel (28) or Gaviscon liquid (25). 10 ml qds for eight weeks. Symptom assessment and endoscopy were performed at the start and end of the study. Both groups were comparable for age and sex distribution, alcohol and tobacco consumption, baseline symptoms, endoscopy and biopsy scores and withdrawals (three per group). After eight weeks treatment both agents significantly (p<0.01) improved symptoms. Asilone gel (79%) being significantly (p<0.05) superior to Gaviscon liquid (52%) in relieving heartburn. Only Asilone gel (38%) produced a significant (p<0.02) improvement in endoscopic oesophagitis from baseline scores. Asilone was also superior to Gaviscon (29% vs 8%) in improving histological scores but this difference was not statistically significant (0.05<p<0.06).

The findings of this study suggest that Asilone gel is superior to Gaviscon liquid in the treatment of reflux oesophagitis.

Gastric adaptive relaxation in patients with gastro-oesophageal reflux

M N Hartley, S J Walker, and C R Mackie (University Department of Surgery, Royal Liverpool Hospital, Liverpool)

Gastric adaptive relaxation (GAR) may play a role in the pathophysiology of gastro-oesophageal reflux (GOR). We measured GAR in 13 normal healthy volunteers (HV) and in 12 patients with GOR confirmed by 24 h pH monitoring. The HV group were: 11 men, two women; mean age 30 years, range 22-41 years; mean body weight 67 kg, range 50 to 75 kg. All were asymptomatic on no medication. The GOR group were: eight men, four women; mean age 47 years, range 23-65 years; mean body weight 78 kg, range 60-92 kg. All received no medication 12 hours before the study. Endoscopy was normal in five, showed hiatus hernia with oesophagitis in four and oesophagitis only in three.

Fasted subjects were intubated with a Ryle’s tube containing a pressure microtransducer and with a flaccid plastic bag (800 ml) attached. Gastric corpus fundus pressure was recorded during distension of the bag with 460±30 ml (mean±SD) of air over 30 seconds. Pressure indices (median: range) derived from areas under the pressure curves were: HV: 12.7 (7.5-17.1) cm H2O and GOR: 9.1 (6.4-13.3) cm H2O (p<0.02 Mann Whitney U test). No correlation was found between pressure indices and age, sex or body weight.

The result was unexpected. It is, however, consistent with reports of delayed gastric emptying in patients with GOR.

Patterns of acid reflux in complicated oesophagitis

D A Robertson, M Aldersley, H Shepherd, and C L Smith (Department of Medicine II, Southampton General Hospital, Southampton) Oesophageal manometry and 24 h ambulatory pH recordings from the distal oesophagus were performed in 25 patients with complications of oesophagitis (stricture, Barrett’s oesophagus or oesophageal ulcer) and compared with 25 patients with uncomplicated oesophagitis.

Acid reflux was more severe in the complicated group with 26-2% of time below pH 4 compared with 11-3% in uncomplicated patients (p<0.01). This difference was most marked at night, when complicated patients had long periods of acid reflux with 35-6% of time less than pH 4 compared with 5-2% in uncomplicated patients (p<0.001). The mean duration of nocturnal acid reflux was 15-4 minutes (2-1 minutes uncomplicated, p<0.001). Oesophageal motility was markedly abnormal in both groups, but with no demonstrable differences in lower oesophageal sphincter pressure (24 mm Hg complications, 31 mm Hg oesophagitis, NS) or peristalsis (37% abnormal waves complications, 34-5% oesophagitis NS) between the groups. Oesophageal dilatation was associated with a non-significant increase in acid reflux (20-3% to 31-4%).

Patients with complications of oesophagitis have different patterns of acid reflux from uncomplicated patients, with prolonged nocturnal bathing of the oesophageal mucosa which may be the cause of stricture formation, metaplasia or ulceration.

Healing and relapse of reflux oesophagitis after treatment with omeprazole 20 mg or 40 mg daily

D J Hetzel, J Dent, W Reed, F Narivelva, M MacKinnon, and B Laurence (Dept.
Adelaide Hospital, and Repatriation Hospital, Gastroenterology and of all double oesophagitis was considered normal. Six of these had abnormal oesophageal acid exposure. The remaining 12 patients had abnormal gastric profiles. In six, gastric hypersecretion was correctly predicted and in one achlorhydria was diagnosed. The other five patients had abnormal alkaline shifts suggestive of duodenogastric reflux confirmed by reflux during radionuclide cholecintigraphy in three patients, two of whom had oesophagitis but normal acid exposure.

Combined pH monitoring is useful in the early evaluation of upper gastrointestinal symptoms. It can reliably predict abnormalities of gastric secretion and can identify patients whose gastriits and oesophagitis might be associated with reflux of duodenal fluid.

Influence of hiatal hernia on oesophageal function

L R Jenkinson, T L Norris, and A Watson
(Department of Surgery, Royal Lancaster Infirmary, Lancaster, UK and Creighton University, Omaha, Nebraska, USA)

Twenty patients with gastro-oesophageal symptoms underwent combined 24 hour pH monitoring of the oesophagus and stomach. Twenty asymptomatic volunteers with normal barium radiology also had combined monitoring and provided a control group. Diet, medication, body position and physical activity were controlled. Oesophageal acid exposure was calculated as per cent time spent <pH 4. The effects of meals were excluded from the gastric pH profile and using the remaining data, gastric alkaline shift (per cent time >pH 4) and acid shift (per cent time <pH 2) were obtained.

In eight patients the gastric data were considered normal. Six of these had abnormal oesophageal acid exposure. The remaining 12 patients had abnormal gastric profiles. In six, gastric hypersecretion was correctly predicted and in one achlorhydria was diagnosed. The other five patients had abnormal alkaline shifts suggestive of duodenogastric reflux confirmed by reflux during radionuclide cholecintigraphy in three patients, two of whom had oesophagitis but normal acid exposure.

Combined pH monitoring is useful in the early evaluation of upper gastrointestinal symptoms. It can reliably predict abnormalities of gastric secretion and can identify patients whose gastriits and oesophagitis might be associated with reflux of duodenal fluid.

Clinical applications of simultaneous 24 hour ambulatory gastric and oesophageal pH monitoring

C S Ball, T L Norris, A Watson, and T R Demeester
(Department of Surgery, Royal Lancaster Infirmary, Lancaster, UK and Creighton University, Omaha, Nebraska, USA)

Twenty patients with gastro-oesophageal symptoms underwent combined 24 hour pH monitoring of the oesophagus and stomach. Twenty asymptomatic volunteers with normal barium radiology also had combined monitoring and provided a control group. Diet, medication, body position and physical activity were controlled. Oesophageal acid exposure was calculated as per cent time spent <pH 4. The effects of meals were excluded from the gastric pH profile and using the remaining data, gastric alkaline shift (per cent time >pH 4) and acid shift (per cent time <pH 2) were obtained.

In eight patients the gastric data were considered normal. Six of these had abnormal oesophageal acid exposure. The remaining 12 patients had abnormal gastric profiles. In six, gastric hypersecretion was correctly predicted and in one achlorhydria was diagnosed. The other five patients had abnormal alkaline shifts suggestive of duodenogastric reflux confirmed by reflux during radionuclide cholecintigraphy in three patients, two of whom had oesophagitis but normal acid exposure.

Combined pH monitoring is useful in the early evaluation of upper gastrointestinal symptoms. It can reliably predict abnormalities of gastric secretion and can identify patients whose gastriits and oesophagitis might be associated with reflux of duodenal fluid.

Cisapride improves oesophageal transit in patients with dysphagia. Results of a randomised double-blind crossover trial

C A Eriksen, D Sutton, N Kennedy, and A Cusieri
(Departments of Surgery and Nuclear Medicine, Ninewells Hospital and Medical School, Dundee, Scotland) Oesophageal dysphagia is a distressing symptom and sometimes difficult to treat. In a randomised double blind crossover trial, we assessed the efficacy of cisapride, a synthetic gastrointestinal prokinetic drug, in relieving dysphagia. Symptomatic patients with primary motility disorders (n=13) and reflux oesophagitis (n=13) were treated for two week periods with cisapride then placebo or vice versa. Before and after each treatment course, symptom score was evaluated, and solid bolus oesophageal transit time, 24 hour oesophageal pH monitoring and endoscopy were performed. Although cisapride produced an improvement in symptoms, the effect was not statistically different from the placebo effect. The total oesophageal transit time was significantly (p<0.008) improved in 17 patients (65-4%) after cisapride compared with after placebo. There was no significant change in endoscopic grading after either drug. Oesophageal pH monitoring showed some improvement in supine acid exposure after cisapride (pH<4; cisapride 4-2%, placebo 16-5%; mean % data points), but these differences compared with placebo were not significant. These preliminary results demonstrate a significant improvement in the oesophageal transit of dysphagic patients after treatment with cisapride.

Effects of cisapride (C) upon responses of the oesophagus to distension

W G Case
(University Department of Surgery, The General Infirmary, Leeds) Gastro-oesophageal reflux (GOR) produces oesophageal distension, peristalsis and subsequent acid clearance. Cisapride (Janssen Ltd) reduces the duration of nocturnal acid reflux in patients with GOR. Does it affect oesophageal responses to intraluminal distension? This has been investigated in 14 healthy male volunteers age 21 years (19-33). With subjects starved and supine, manometry traces were recorded from upper oesophageal sphincter and 8 and 14 cm in the oesophageal body by means of a Gaeltte catheter passed per nares. The catheter tip in the distal oesophagus carried a balloon which was inflated with 5 ml water to stimulate oesophageal...
motility. Frequency, duration and amplitude of primary peristalsis (PP), secondary peristalsis (SP), and tertiary contractions (TC) at 14 cm were quantified for one minute after balloon inflation under baseline conditions, and again after intravenous injection of 10 mg C. Traces were analysed blind with regard to treatment. While C had no significant effects upon PP or TC, SP was significantly stimulated, SP/min increased from 0 (0-1) to 1 (0-4)*, with a duration/ min of 0 (0-1.8) increasing to 3.3 (0-10.7) sec* and a maximal amplitude increasing from 0 (0-20) to 37.5 (0-180) cm H2O* after injection of C. The drug may therefore reduce nocturnal acid reflux time by stimulation of SP. (All data as median and range, *p<0.01, Wilcoxon signed rank test.)

Manometric findings in patients with the globus sensation

J C Linsell, A Anggiansah, and W J Owen (Department of Surgery, Guy's Hospital, United Medical and Dental Schools, St Thomas St, London) Studies using water perfused oesophageal manometry systems have suggested that the globus sensation may be a manifestation of an oesophageal motility disorder either of the oesophageal sphincters or of the body of the oesophagus. Using a Gaeltic system of six introesophageal microtransducers we have performed manometry on 18 patients (median age 53 years) whose major symptom was 'globus' and who had normal oesophascopy and indirect laryngoscopy. Using a station pull through technique the mean lower oesophageal sphincter pressure (LOS) was significantly lower in the globus patients than in 12 normal controls (p<0.02 using Wilcoxon's rank-sum test). Four patients had abnormal motility of the oesophageal body; two having diffuse oesophageal spasm and two non-specific motility disorders. There was no significant difference between upper oesophageal sphincter pressures in either globus patients or controls. Three patients had abnormalities of upper oesophageal sphincter function. Our findings suggest that patients with the globus sensation do have oesophageal abnormalities. The finding of hypotensive LOS pressures suggests a possible association with gastro-oesophageal reflux.

Dysphagia for solids is a longterm effect of the Angelchik antireflux prosthesis

C S Robertson, D L Morris, S Amar, and J D Hardcastle (Department of Surgery, University Hospital, Nottingham) Dysphagia for solids is a common problem following antireflux operations and we have previously reported a high incidence after insertion of the Angelchik antireflux prosthesis (ACP). To study this problem we have performed a marshmallow/barium swallow (MMBS) in the early postoperative period and at subsequent follow up. The oesophageal transit time of the marshmallow was recorded (normal <1 min). Of 40 patients we have initial post operative MMBS in 36 patients and of these 24 (66%) were prolonged. We have then repeated the MMBS in 21 patients at a median of 33 months (9-48) and this long term MMBS was prolonged in 15/21 patients (71%). In addition three patients had the ACP removed for severe dysphagia before repeat examination was performed. Of eight patients with a normal MMBS postoperatively seven of these remained normal at long term follow up and of 13 patients with prolonged transit postoperatively, all remained abnormal. We conclude that oesophageal transit of solids is significantly slowed by the ACP in many patients and that this is not a transient postoperative phenomenon.

Expression of normal ranges in 24 hour intra-oesophageal pH monitoring

L R Jenkinson, T L Norris, and A Watson (Royal Lancaster Infirmary, Ashton Road, Lancaster) The advent of 24 hour intra-oesophageal pH monitoring has revolutionised the diagnosis of gastro-oesophageal reflux but there is still no uniform method for the expression of normal ranges. Data from healthy subjects are usually skewed towards zero and the use of the conventional ±2 SD from the mean produces negative lower limits. We have investigated the use of percentiles as an alternative means of expression.

Twenty six healthy volunteers underwent manometry and 24 hour ambulatory pH monitoring. The upper limits of normality were estimated from the 90th percentile. Subjects with two or more abnormal values in either the upright or supine periods were classified as 'refluxers'. Fifty patients with endoscopic oesophagitis were then evaluated using this technique. Two (7.7%) controls were classified as refluxers (specificity =92%) and four patients as normal (sensitivity=92%). The positive and negative predictive values were 93% and 86% respectively.

We conclude that percentiles provide a useful means of estimating normal ranges which demonstrate high sensitivity and specificity.

Transabdominal colon interposition for benign oesophageal stricture

P E Burke, E McGovern, and K M Shaw (Introduced by G McEntee) (Royal City of Dublin Hospital, Baggot Street, Dublin) Thirty four consecutive cases of transabdominal oesophageal resection with colon interposition were reviewed. There were 20 men and 14 women ranging in age from two to 83 years (mean 51.4). Causes of strictures included: reflux oesophagitis (30), corrosive ingestion (two), achalasia (one), and tracheo-oesophageal fistula (one). The mean duration of symptoms was five years, and 18 patients had previous unsuccessful surgery. A left thoracotomy with the left colon mobilised through the diaphragm was always performed. There was one postoperative death (2.9%). Six postoperative complications developed (17.6%), only three of which were attributable to the thoracotomy. No anastomotic breakdown occurred. Three recurrent strictures developed (9%): two oesophageocolic in children, which were revised surgically, and one gastrocolic in an adult which required a single dilatation. Four patients were lost to follow up, and five were asymptomatic until death. Over 70% of patients have been symptom free during a mean follow up period of eight years and all are satisfied with the result of their operation. Thoracotomy for oesophageal resection and left colon interposition is associated with few postoperative intrathoracic complications and does not predispose to proximal stricture formation in adults. The high level of patient satisfaction confirms that the left colon is an excellent vascular oesophageal substitute.

Laparoscopy, ultrasound or CT in the detection of intra-abdominal metastases for oesophageal cancer?

J Watt, Dorothy Anderson, I Stewart, G Bell, and J R Anderson (Departments of Surgery and Radiology, Glasgow Royal Infirmary and Inverclyde Hospital, Greenock) A number of non-operative options are now available for the palliation of obstructing carcinomas of the oesophagus or cardia. The accurate identification of intra-abdominal dissemination is therefore important in planning management.
This prospective study evaluates the accuracy of ultrasound, CT and laparoscopy in 51 patients with tumours of the oesophagus or cardia. There were 28 men and 23 women, aged 41–93 years (mean 65) of whom 26 had squamous and 25 adenocarcinomas. All patients underwent three investigations and 43 subsequent laparotomy. Eleven patients had histologically proven hepatic metastases (seven at laparotomy+four laparoscopy/biopsy), 24 had nodal metastases and five omental/parietal metastases. Ultrasound correctly identified five hepatic and four nodal metastases (sensitivity 45% and 16%); CT six hepatic and seven nodal metastases (sensitivity 54% and 29% respectively). Laparoscopy identified nine hepatic and 13 nodal metastases (sensitivity 81% and 54%). In addition laparoscopy identified five omental/parietal metastases not detected by either of the other modalities. Laparoscopy offers a safe accurate means of assessing intra-abdominal spread of oesophageal/cardia tumours and may obviate the need for surgery in some patients.

Barrett’s oesophagus: risk factors for malignancy

P GILLEN, P KEELING, AND T P J HENNESSY (Department of Surgery, St James’s Hospital, Dublin, Ireland) Barrett’s oesophagus is generally accepted as a consequence of gastrooesphageal reflux and has a potential for malignant change. The frequency of malignant change makes identification of causative factors difficult. To assess whether patients with Barrett’s and associated oesophageal adenocarcinoma differ from patients with benign Barrett’s epithelium, 42 Barrett’s patients – 24 benign (BB) and 18 malignant (MB) – have been studied over a five year period.

The mean ages (65.0 BB v 65.5 MB) and male:female ratio were similar in both groups. Heartburn was significantly more common in the benign group (24 BB v 4 MB p<0.001). Dysphagia (10 BB v 16 MB), presence of hiatal hernia (9 BB v 3 MB) and smoking and alcohol consumption did not differ significantly between the two groups. Duration of oesophageal symptoms was significantly longer (p<0.001) in the benign group (median two years, range 1–20 years) than the malignant group (median eight weeks, range 4–52 weeks).

Dysplastic change was observed in adjacent Barrett’s epithelium in six patients with malignancy and only one in the benign group (p<0.05). Specialised intestinal-type epithelium was present in all malignant cases but was seen in only 12 benign cases (p<0.001).

Malignant Barrett’s patients more frequently have specialised intestinal type epithelium and associated dysplastic change which, if present in a benign setting, may predict future malignant change and should be closely monitored.

Oesophageal cytology and biopsy: before or after dilatation?

H J O’CONNOR, A SAVAGE, H THOMPSON, R M VALORI, E COLE, AND R COCKEL (Departments of Gastroenterology and Histopathology, Selby Oak Hospital, Department of Histopathology, General Hospital, Birmingham) Although it is now routine practice to take tissue specimens and dilate oesophageal strictures at a single sitting, there are no data on whether cytology and biopsies are best taken before or after dilatation. In this study, 32 consecutive patients (17 M:15 F, 42–89 yrs) with oesophageal stricture (mean lumen size, 4 mm) had brush cytology and biopsies (three) taken before and after dilatation (Celestin dilators). Specimens were coded and cytology and histology assessed blindly by separate pathologists.

Of the 32 patients, five had malignant and 27 benign strictures. In the malignant group, cytology and biopsy gave one false-negative result each before but dilatation but were diagnostic in all cases after dilatation. There were no false-positive cytology or histology results before or after dilatation in the benign group. Dilatation had no significant effect on biopsy size or the rate of detection of normal, inflamed or ulcerated squamous epithelium or necrotic debris. Columnar lined oesophagus was, however, more readily detected after dilatation, being found in 21 patients compared with only 10 before dilatation (χ², p<0.01).

Our results suggest that in the evaluation of oesophageal structures higher diagnostic yield and accuracy is obtained from tissue specimens taken after dilatation.

Longterm treatment with omeprazole (OME) in resistant refluxoesophagitis: effects on endoscopic healing and fasting serum gastrin (G) levels

E C LINKENBORG-KNOL, J B M JANSEN, J W DE BRUYNE, G F NELIS, H P M FESTEN, P SNEL, A E G LÜCKERS, AND S G M MEUWISSEN (Depts of Gastroenterology, Free Univ Hospital Amsterdam, State University Leiden, Slotervaart Hospital, Amsterdam, Sophia Hospital Zwolle, Groot Ziekenhuis Den Bosch, RZK Dordrecht, The Netherlands) We studied the efficacy and safety of longterm treatment of OME in 35 patients (24 M, 11 F, mean age 66 yr, range (R) 42–87) with severe refluxoesophagitis, who were resistant to treatment for at least 12 weeks with cimetidine 1-6 g or ranitidine 0-6 g. In 16 patients complications (bleeding or strictures) had occurred, eight underwent previously antireflux surgery. After 4–12 weeks of 40 mg OME od all patients were healed; then OME was reduced to 20 mg od as maintenance (M). The study included clinical, endoscopic and biochemical follow-up (every four weeks in the healing period, every three months in M-period). Until May 1987 31/35 (89%) patients were still healed after at least six months M-treatment (mean 11.7, R:6–16 months). Refluxoesophagitis recurred in four cases (after 1, 2, 9, and 9 months respectively). All four healed again with OME 40 mg. G-levels (N<1000 pg/ml) increased from median 60 (R:6–185) at pre-entry to median 90 (R:10–378) after four weeks OME 40 mg. In the M-period (OME 20 mg) no fall in G-levels occurred: after 12 months the median value was 180 (R:14–573). No other relevant clinical or biochemical side-effects occurred.

OME-therapy is highly effective, both in healing as well as in the prevention of recurrences of H₂ receptor resistant refluxoesophagitis.

OME 40 mg produces a significant rise of fasting G-levels, remaining persistently raised up to 12 months despite dose reduction to 20 mg.

Value of endoscopic surveillance in the early detection of malignant change in Barrett’s oesophagus

C S ROBERTSON, J F MAYBERRY, P D JAMES, AND M ATKINSON (Department of Surgery and Pathology, University Hospital, Nottingham) Estimates of the risk of adenocarcinoma developing in Barrett’s columnar lined oesophagus vary greatly and most data previously presented have been based on prevalence. We present a prospective study of 56 patients with columnar lined oesophagus diagnosed in the 10 year period between 1977 and 1986 and followed up with regular endoscopy, and biopsy. Of the 56 patients 31 were men, their mean age was 62 years (range 22–84) and the mean follow up was three years. During follow up the squamous-columnar mucosal junction was observed to
progress up the oesophagus in 11 patients but such progression did not increase the risk of malignancy ($\chi^2=0.94; p=ns$). During the study eight patients developed severe dysplasia in the columnar epithelium, two progressed to carcinoma \textit{in situ} and in three patients an invasive adenocarcinoma developed. Diagnosis depended largely upon biopsy evidence, as in only one of the three patients was there macroscopic evidence of malignancy. These figures indicate that carcinoma occurred once in every 56 patient years follow up, and the relative risk was 67 times greater than that of the general population of this age and sex distribution. These findings provide clear evidence that endoscopic surveillance is important in the early detection of malignant change complicating Barrett's oesophagus.

**Palliation of malignant oesophageal strictures: preliminary comparison of Atkinson tube and ACM1 tumour probe in two centres**

A S MCINTYRE, D L MORRIS, C S ROBERTSON, L SLOAN, J HARRISON, W R BURNHAM, AND M ATKINSON (Dept Gastroenterology, Oldchurch Hospital, Essex and Dept Surgery, University Hosp, Nottingham) We have compared tumour debulking by electrocoagulation with the tumour probe (TP) and Atkinson tube insertion (AT) in 27 patients with malignant oesophageal strictures. Palliation of dysphagia was assessed subjectively and objectively by barium swallow+timed solid swallows (11 patients). Thirteen patients received an Atkinson tube (Squam/Adeno/Extrinsic 4/6/3) and 14 the tumour probe (5/7/2). Stricture was upper (AT-1, TP-2), middle (AT-8, TP-2) or lower (AT-4, TP-10). Three patients were transferred from their initial treatment groups: one AT to TP (tube displacement), two TP to AT (one refused repeat endoscopies, one probably undertreated).

Probe treated patients ate a more varied diet, though timed solid swallows showed no difference between the groups (95% conf limit AT v TP $-3.6$ to $9.0 v -0.4$ to $2.2$ mm/sec). Six patients required repeated probe therapy. Complications seen: Atkinson tube group – two perforation (one pre-insertion dilatation), two tubes displaced, two obstructed by food; Probe group – one perforation (pretreatment dilatation), one persistent dysphagia.

The tumour probe and Atkinson tube give comparable palliation and appear complimentary. The probe offers an alternative for high or low oesophageal lesions, though repeated treatment may be necessary.

**SMS 201-995 in the management of variceal bleeding**

R K MCKEE, S D PRINGLE, O J GARDEN, A R LORIMER, AND D C CARTER (University Departments of Surgery and Medical Cardiology, Royal Infirmary, Glasgow) Pharmacological arrest of bleeding from oesophageal varices remains a desirable but elusive goal. A long acting somatostatin analogue SMS 201-995 has been studied in this context.

Sixteen stable cirrhots had wedge and free hepatic venous pressure measured using a Swan-Ganz catheter. Nine patients given a 60 minute intravenous infusion of 25 $\mu$g/h of SMS 201-995 had a 30% fall in transhepatic venous gradient which was not seen in 7 patients who did not receive the drug.

Twenty two patients with endoscopically proven active variceal bleeding were randomised to 48 hours of treatment with oesophageal tamponade or intravenous infusion of SMS 201-995. Initial control was achieved in all 11 patients treated with tamponade and nine of 11 patients given SMS 201-995. Complete control of bleeding over 48 hours was achieved in eight of the tamponade group and six of the SMS 201-995 group. These differences are not statistically significant. SMS 201-995 may aid temporary control of variceal bleeding while more definitive treatment is being arranged.

**Can metoclopramide arrest active bleeding from varices? A prospective controlled trial**

S W HOSKING, W DOSS, H EL-ZEINY, M S BARSOUm, AND A G JOHNSON (Kasr El Aini Hospital, Cairo and Royal Hallamshire Hospital, Sheffield) Active bleeding is still present in 30% of patients reaching hospital after variceal haemorrhage. Balloon tamponade, vasoactive therapy or immediate sclerotherapy are not always available or effective and an alternative simple measure is needed. Previous studies have shown that pharmacological constriction of the lower oesophageal sphincter (LOS) causes a marked reduction in flow and pressure in submucosal varices proximal to LOS. As 90% of variceal bleeds occur within the zone encircled by the LOS, we investigated whether such constriction would arrest active variceal bleeding.

Twenty patients with endoscopically proven oesophageal variceal bleeding originating from within 2 cm of the OG Junction, were randomised to receive either 20 $\mu$g metoclopramide iv or placebo in a double blind manner. Fifteen minutes after administration each patient was re-endoscoped to document whether bleeding had stopped. All patients then received sclerotherapy. Of the 10 patients who received metoclopramide, nine had stopped bleeding compared to four of the 10 who received placebo (p<0.01).

These results confirm that LOS constriction effectively tamponades bleeding varices. Metoclopramide may be a simple method of arresting variceal bleeding but in patients requiring transfer to specialist centres, longer acting drugs may be necessary.

**Biphasic diurnal pattern of onset of bleeding from oesophageal varices**

D SPRENGERS, F D’HEGRE, D COOK, P A MCCORMICK, N MCINTYRE, AND A K BURROUGHS (Royal Free Hospital School of Medicine and Clinical Epidemiology, London) Over a 42 month period we collected prospectively data on 521 separate bleeding episodes in 265 cirrhotics, defined as haematemesis or melaena with a 2 gd/dl drop in haemoglobin or change in vital signs. Time of onset of melaena or haematemesis was recorded accurately because of our interest in prognostic variables for variceal bleeding which may include interval between onset and admission. The source of bleeding was oesophageal varices in 417 episodes of which the time of onset was available in 397: 114 (29%) with only melaena and 232 (58%) with only haematemesis before admission. The 24 hourly distributions showed a biphasic pattern with 46% of the bleeds occurring between 7 and 10 am (n=107) and between 20 and 22 pm (n=76). The Poisson heterogeneity test (Armitage 1972: p 214) was used to assess non random distribution assuming that the onset of bleeding would be equally distributed, throughout 24 hours. The asymmetric distribution was significant for the whole groups (p<0.001) and for the subgroups: haematemesis only (p<0.01) and melaena only (p<0.001). The time of onset was the same for patients who started bleeding in hospital or at home.

We do not have an explanation for this observation but clearly the biphasic diurnal pattern of onset of bleeding from oesophageal varices in cirrhotics may have
relevance to the pathogenetic mechanisms related to variceal bleeding.

**Quantitative 99m-Tc DISIDA scanning in sphencter of Oddi dysfunction (SOD)**

G M Fullarton, W R Murray, and T Hilditch (Departments of Surgery and Nuclear Medicine, Western Infirmary, Glasgow)

Sphincter of Oddi dysfunction (SOD) is a recognised cause of postcholecystectomy pain but is a difficult condition to diagnose requiring endoscopic biliary manometry (EBM) to confirm sphincter motor abnormalities. We have assessed quantitative cholescintigraphy in patients with clinical and manometric evidence of SOD to determine its value as a non-invasive screening test.

Eight postcholecystectomy (PC) patients with clinical and manometric evidence of SOD underwent quantitative 99mTc DISIDA scans (group 1). Eight PC patients with non-biliary type abdominal pain (group 2) and eight asymptomatic PC patients acting as controls (group 3) also underwent DISIDA scanning. Scintigraphic analysis demonstrated that the T-max (time in minutes to maximum counts) was significantly increased in group 1 compared with both group 2 (25.9±2.1 vs 15.0±1.5, mean±SEM, p<0.01) and group 3 (25.9±2.1 vs 13.0±2.0, p<0.01). It was also noted that the T-max values for group 1 did not overlap with either those of group 2 or 3, SOD patients always having values greater than the highest group 2 or 3 patient.

We conclude that quantitative cholecintigraphy may be a valuable, non-invasive screening test in clinically suspected SOD.

**Studies using the CCK-receptor antagonists CR 1409 point to an important role for cholecystokinin in the stimulation of pancreatic enzyme secretion by bombesin and a meal**

A J D Le Jong, N V Singar, J R M Jansen, and C B H W Lamers (Dept Gastroenterology-Hepatology, Universities of Nijmegen, Essen and Leiden, FG R and The Netherlands)

Pancreatic enzyme secretion is assumed to be mediated by both hormonal and nervous mechanisms. The development of an in vivo active specific CCK-receptor antagonist (CR 1409) enabled us to determine the role of cholecystokinin (CCK) in the regulation of bombesin and meal stimulated pancreatic enzyme secretion. Six conscious dogs, equipped with a gastric fistula and a cannulated pancreatic duct, were studied for one hour basally and two hours after intragastric instillation of a standard test meal or infusion of 90 pmol/kg bombesin or 30 pmol/kg caerulein. In these studies either 2 mg/kg CR 1409 or saline were infused in random order.

Peak plasma CCK concentrations were similar after the meal and during the infusions of bombesin and caerulein. 7.2±0.8, 8.6±0.8 and 8±1±1.2 pM, respectively. Basal pancreatic protein secretion was not significantly affected by CR 1409 (251±64 mg/30 min during saline and 163±44 mg/30 min during CR 1409). CR 1409 strongly inhibited postprandial pancreatic protein secretion from 789±119 to 440±73 mg/30 min (p<0.05), bombesin-stimulated pancreatic protein secretion from 32±210 to 255±37 mg/30 min (p<0.05), and caerulein-stimulated pancreatic protein secretion from 1274±236 to 442±147 mg/30 min (p<0.01). The CCK-receptor antagonist did not significantly influence pancreatic volume or bicarbonate secretion.

These studies show that CCK plays an important role in the regulation of meal and bombesin stimulated pancreatic enzyme secretion, but is of little significance for the regulation of basal enzyme secretion and for both basal and postprandial pancreatic bicarbonate secretion.

**Effect of bombesin on serum trypsin after various forms of gastric surgery**

J Kreuning, J B M J Jansen, and C B H W Lamers (Dept Gastroenterology-Hepatology, University Hospital Leiden, The Netherlands)

Infusion of bombesin stimulates several gastrointestinal functions including pancreatic enzyme secretion. As postprandial pancreatic enzyme secretion is reduced not only in patients with pancreatic insufficiency but also in some patients with previous gastric surgery, we have studied the effect of infusion of bombesin (60 pmol/kg/min) on serum trypsin levels in 10 patients with truncal vagotomy, nine with parietal cell vagotomy, eight with Billroth I-gastroctomy, 14 with Billroth II-gastroctomy and 11 with gastrectomy and Roux-en-Y anastomosis, and we have compared the results with those of nine patients with pancreatic insufficiency and 11 normal control subjects. Blood was obtained before and at the end of the infusion and serum trypsin concentrations were measured by radioimmunoassay. Results, expressed as median and range, were analysed by Wilcoxon’s rank sum test.

Incremental serum trypsin in the patients with parietal cell vagotomy (453; 65–20 385 μg/l), Billroth I-gastroctomy (486; 115–870 μg/l), Billroth II-gastroctomy (619; 51–1002 μg/l), and gastrectomy with Roux-en-Y anastomosis (317; 19–950 μg/l) were not significantly different from the results in the normal subjects (697; 199–9795 μg/l). However, in the patients with truncal vagotomy incremental serum trypsin (140; 8–430 μg/l) was significantly lower.
An abnormally low serum trypsin response to bombesin is found not only in patients with pancreatic insufficiency but also in patients with truncal vagotomy. The latter finding underlines the importance of an intact innervation of the pancreas for the serum trypsin response to bombesin.

Therapeutic fresh frozen plasma (FFP) in acute pancreatitis: intravenous or intraperitoneal?

A J Goodman, N C Bird, and A G Johnson
(University Surgical Unit, Royal Hallamshire Hospital, Sheffield) In acute pancreatitis, plasma and peritoneal levels of $\chi^2$ macroglobulin ($\chi^2$ M) fall; molecular size limits its access to the peritoneal cavity where its saturation coincides with death, despite there still being unbound $\chi^2$ M in the circulation. Fresh frozen plasma, a source of $\chi^2$ M was administered either intravenously or intraperitoneally in a rat model of acute pancreatitis. Rats were randomly divided into six groups of 21 animals. All received 14 ml of dextrose/saline by continuous intravenous infusion (IVI) each 24 hours. Additionally, groups a, b, c received 10 ml of normal saline, Haemaccel® or rat FFP respectively 10 ml over 24 hours. Groups d, e, f received the same 10 ml additions but as a daily intraperitoneal bolus. These regimens were repeated for three days. No saline control survived 72 hours. Intravenous Haemaccel® or FFP improved survival (38%, 48%, p<0.01). Intraperitoneal Haemaccel® was ineffective whereas FFP improved survival further to 62% compared with saline controls (p<0.001). Although this was not a significant improvement over IV FFP, the intraperitoneal route would allow larger volumes of FFP to be administered.

These results suggest two mechanisms for the improvement: (1) a non-specific effect of iv colloid, (2) supplementation of declining $\chi^2$ M levels by FFP especially within the peritoneal cavity.

Illness scoring systems—improved precision for monitoring the progress of acute pancreatitis?

M Larvin, and M J McMahon (University Department of Surgery, The General Infirmary, Leeds) Evaluation of potential therapy for acute pancreatitis (AP) is severely limited by the heterogeneous nature of the attacks, wide variation in severity and the lack of end-points by which to monitor progress. Systems of multiple criteria have been developed for prognosis, but are imprecise and provide information only during the initial stages of the attack. We have prospectively evaluated three illness scoring systems in 149 attacks of AP, relating the data obtained to clinical severity as defined by predetermined criteria. Thirty-five attacks were classified as severe (11 deaths, 24 major complications), and 114 as mild. Ranson and Imrie scores were calculated within 48 hours of admission, and the Acute Physiology-II Score (APSI-II). Simplified Acute Physiology Score (SAPS) and MRC Sepsis Score (MRCS) were calculated daily. From data available at 48 hours after admission, the overall diagnostic accuracy for APS-II was 90%, Imrie scores 83%, Ranson scores 79%, and 78% for SAPS and MRCS scores. At later stages of the attack, dynamic assessment of serial APACHE-II scores predicted late complications with a sensitivity of 81% and specificity of 96%. These results suggest that the APS-II illness scoring system has the potential to provide improved objective measurement of severity and progress of AP.

Experimental studies on interstitial hyperthermia for treating pancreatic cancer

A C Steger, H Barr, R Hawes, S G Bown, and C G Clark (National Medical Laser Centre, Department of Surgery, University College London, The Rayne Institute, London) Most pancreatic cancers are unresectable at presentation and only palliative treatment is possible. Interstitial low power hyperthermia has the potential to destroy these tumours. We studied the nature and evolution of local thermal necrosis in normal canine pancreas produced by the insertion of a 0.4-mm flexible quartz fibre from a low power Nd:YAG laser, either up a pancreatic duct or directly into the bulk of the gland. The extent and severity of the necrosis depended on the laser power and exposure time used. Some animals developed a lethal pancreatitis, particularly if the duct was ruptured. At 1 or 1.5 W, lesions up to 1.7 cm in diameter, however, could be produced which healed safely.

The use of multiple (four) fibres inserted 1 cm apart (in a square shape) and activated simultaneously a 1 W each for 1000 sec produced a lesion up to $7 \times 5$ cm in size in the head of the gland. which healed safely with contraction and scarring of that area of the gland. Hyperamylasaemia was found in all animals, but, clinical pancreatitis was mild. Pancreatic tumours are more fibrous than normal gland and so after thermal necrosis are likely to heal better, making this technique worthy of further investigations for treating pancreatic cancer.

A non-isotopic test for pancreatic insufficiency which distinguishes small bowel malabsorption

I M Chesner, J D Berg, and N Lawson (East Birmingham Hospital and Sandwell Hospital West Midlands) We have previously demonstrated that para-amino salicylic acid (PAS) is potentially a more practical substance than 14C-PABA when used to derive a PABA/PAS excretion index.

We have now compared these excretion indices in 32 subjects including several with small bowel malabsorption. In 16 with exocrine insufficiency as judged by the 14C-PABA/PABA ratio the mean (SD) excretion index was 14 (8). Using PAS/PABA ratio the mean excretion (SD) index was 13 (7). There was excellent correlation between the two assay methods r=0.92 p<0.01. The sensitivity of the PAS/PABA excretion index was 95% and its specificity 85%. Predictive value of test 86%.

In patients with small bowel malabsorption (eight) the mean excretion index was reduced with a mean (SD) of 55 (13) and the percentage amounts of PAS and PABA recovered were reduced. Not one of the subjects with small bowel disease had excretion indices as low as those with pancreatic malabsorption, however.

We conclude that the PAS/PABA excretion ratio is a rapid, non-isotopic one day test of pancreatic exocrine function and can distinguish between pancreatic insufficiency and small bowel malabsorption. The non-isotopic nature of this test makes it more widely applicable and repeatable in the same individual.

Endoscopic ultrasound of pancreatic disorders

P J Shorvon, W R Lees, R A Frost, and L M Daws (Radiology Department, The Middlesex Hospital, London) Endoscopic ultrasound (EUS) is performed in a similar manner to routine upper GI endoscopy, but uses a specially constructed endoscope with an ultrasound transducer incorporated into
its tip. Intraluminal bowel gas and bone are by-passed by this technique. By applying a high frequency transducer within a few millimetres of the pancreas, high resolution images of the entire pancreas and adjacent organs are obtained in over 90% of patients. The resolution achieved is better than any other cross-sectional imaging technique.

Endoscopic ultrasound is employed in the 10–20% of cases of pancreatic disorders in which important imaging questions remain after standard investigations. We have done over 100 such examinations, and this paper illustrates by case studies the value of the technique for each of the six main reasons of referral: (1) evaluation of a pancreatic mass of uncertain nature, (2) final staging of small pancreatic neoplasm prior to surgery, (3) localisation of islet cell tumours, (4) evaluation of focal pancreatic duct abnormalities discovered on pancreaticography, (5) evaluation of early chronic pancreatitis, particularly the parenchymal rather than duodenal abnormalities, (6) evaluation of low biliary obstruction of uncertain nature.

In our institution EUS is now the most specific imaging test in the diagnosis of pancreatic disease.

Sex differences in gall stone pancreatitis

T V TAYLOR, S RIMMER, C P ARMSTRONG, S B LUCAS, AND J JIEACOCK (Department of Surgical Gastroenterology, Manchester Royal Infirmary, Oxford Road, Manchester) From a computerised data base comprising 36 pertinent items in each of 664 patients with cholelithiasis, differences were studied between men and women. In 52 patients there was a documented attack of acute pancreatitis (7.8%). Twenty five of 175 men had pancreatitis compared with 27 of 489 women (p<0.0001). Although men with uncomplicated gall stones underwent surgery at a greater age than women they developed pancreatitis earlier (p<0.001). A history of flatulent dyspepsia, chronic cholecystitis and biliary colic was less common in men than women with pancreatitis (p<0.001). Men with pancreatitis had fewer stones in their gall bladders than women (χ²=9.8, p=0.002). The common bile duct and cystic duct in the pancreatic patient were more likely to be dilated (p<0.0001); in the non-pancreatic group these ducts were larger in men. Pancreatic duct reflux on operative cholangiography was more common both in patients with pancreatitis 64% cf 16% (p<0.0001) and in men (p<0.0001). Men are more susceptible to gall stone migration at an early stage of their disease and pancreatic duct reflux. Men have a larger duct system and different anatomical disposition of the sphincter of Oddi which predispose to pancreatitis.

Computer history analysis in acalculous biliary pain

G T SUNDERLAND, R P KNILL-JONES, G P CREAN, AND D C CARTER (University Department of Surgery, Glasgow Royal Infirmary and Diagnostic Methodology Research Unit, Southern General Hospital, Glasgow) The decision to investigate acalculous biliary pain (ABP) rests on the history alone, however, the commonly used ‘biliary history’ has not been defined. We took a detailed history using a computer aided diagnostic system and compared the features present in patients seen and referred for investigation of ABP by general surgeons (n=64) with those of confirmed gallstone disease (n=57) and those present in ‘dyspepsia’ (n=1119).

Acalculous biliary pain patients were diagnosed on a ‘biliary history’ and negative investigations. The decision to operate was based on continued symptoms and 25 have come to cholecystectomy with 85% improved (mean follow up nine months). Of the 39 non-operated patients 38% improved spontaneously, 51% are unchanged and 11% are worse.

Data analysis showed close similarities between ABP and gallstone patients except that gallstone patients had significantly shorter histories and suffered more frequent ‘attacks’ of pain. Acalculous biliary pain patients were quite different to ‘dyspepsia’ patients. There were no differences between patients who had cholecystectomy and those who did not. With the exceptions noted, the symptoms considered important in our population for the diagnosis of biliary disease are present in the history of patients thought to have ABP.

Multivariate analysis of risk factors in patients undergoing surgery and/or endoscopic sphincterotomy (ES) for common bile duct (CBD) stones

J P NEOPTOLEMOS, D E SHAW, B R DAVIDSON, AND D L CARR-LOCKE (Departments of Surgery and Gastroenterology, Leicester Royal Infirmary, Leicester) Multivariate analysis of clinical, laboratory and medical risk factors was undertaken in relation to postoperative outcome in 325 patients undergoing surgery with or without pre-operative ES for CBD stones (group A) and to post-ES complications in 190 patients (group B). Complications occurred in 83 patients (26%) in group A and in 32 (17%) in group B.

By univariate analysis age and serum urea, creatinine, albumin (ALB) and bilirubin (BIL) were all associated with significant complications in both groups (p=0·03 to <0·0001). In group A, however, only BIL, medical risk factors (MRF) and previous use of ES, were independently significant; the probability of complications was logit p=0.51 (MRF)+0.53 (ES)+0·003 (BIL)−1·63 − for example, the probability of complications with BIL=25 μmol/l, MRF and ES both=0 was p=0·17 and with BIL=400 μmol/l, MRF and ES both=1, this was p=0·637. In group B, only BIL and ALB were independently significant; logit p=1·46−0·107 (ALB)+0·004 (BIL) (for example with BIL=25 μmol/l and ALB=40 g/l, p=0·06 and with BIL=400 μmol/l and ALB=20 g/l, p=0·68).

We conclude that (1) all jaundiced patients with CBD stones are at risk, (2) patients with medical risk factors should be treated by ES, alone and (3) ‘fit’ patients are best treated by surgery.

Ingestion of coffee stimulates plasma cholecystokinin secretion and gall bladder contraction in man

B R DOUGLAS, C W KOCH, J R M J JANSSEN, AND C H W LAMERS (Depts Gastroenterology, Hepatology and Radiology, University Hospital Leiden, The Netherlands) It has been noted that there is an association between coffee drinking and carcinoma of the pancreas. Furthermore, ingestion of coffee has been held responsible for the induction of colics in gall stone patients. As cholecystokinin (CCK) has major stimulatory actions on both pancreas and gall bladder, we have studied the effect of coffee on plasma CCK in five healthy volunteers (5 M, age 27–38 yr). After an overnight fast one of three 165 ml isothermal (70°C) and isosmotic (113 mOsm/l) solutions (sodium chloride, caffeinated and decaffeinated coffee) were ingested in random order. Gall bladder volumes were measured by real time ultrasonography and plasma CCK was determined by a sensitive and specific radioimmunoassay at −5, 0, 10, 20, 30, 40, 50, and 60 minutes.

Ingestion of caffeinated coffee induced an increment in plasma CCK of 2·9±1·1 pm (p<0·01) and a reduction in gall bladder volume of 11·0±2·0 cm³ (p<0·01). Decaf-
feinated coffee resulted in lower, though significant (p<0.05), increases in plasma CCK (1.9±0.8 pm) and reductions of gall bladder volume (5.8±1.3 cm³). Ingestion of the sodium chloride solution failed to significantly stimulate plasma CCK release (0.2±0.1 pm) or to induce gall bladder contraction (3.0±4.0 cm³).

Both caffeine and decaffeinated coffee stimulate secretion of CCK and gall bladder contraction. This effect is not mediated by distension or osmotic or thermic factors. The finding that decaffeinated coffee was more potent than decaffeinated coffee indicates that not only caffeine but also other factors are involved in the coffee induced CCK release and gall bladder contraction.

Sphincter of Oddi motility in acalculous biliary pain

G T Sunderland, C G Morrion, and D C Carter (University Department of Surgery, Royal Infirmary, Glasgow) Gall bladder contraction is considered to be the source of symptoms in patients with acalculious biliary pain. Motor abnormalities of the sphincter of Oddi are recognised after cholecystectomy but it is not known whether these disorders result from surgery or pre-exist.

Using ERCP manometry we have examined sphincter motility before cholecystectomy in 18 patients thought to have acalculous biliary pain. The papilla of Vater was cannulated with a triple lumen catheter and a hydraulic capillary infusion system used to perfuse each channel with degassed water. Measurements were made of the frequency of phasic contractions of and basal and peak pressures referenced to duodenal pressure. Eight patients were given bolus intravenous injection of cholecystokinin (1 unit/kg) and recordings repeated three minutes later. Twelve of the 18 patients showed abnormal sphincter motility. Basal pressure ≥30 mm Hg was noted in five patients. Peak pressures of 300 mm Hg and greater were recorded in four patients. Five patients had a frequency of contractions greater than 8/min and paradoxic responses were observed in five of the patients given cholecystokinin. We have shown for the first time prior to cholecystectomy, abnormalities of sphincter motility in patients with acalculous biliary pain.

Gall bladder contraction in patients with irritable bowel syndrome (IBS)

DAN Z BRAVERMAN (INTRODUCED BY M SHINER) (Gastrointestinal Unit, Shaare Zedek Medical Centre, POB 3235, Jerusalem, Israel) Gall bladder contraction (GBC) was measured by real time ultrasound in 20 subjects: eight healthy controls and 12 with irritable bowel syndrome (IBS). The technique was used as previously described (N Engl J Med 1980; 302: 362). The irritable bowel patients were randomly recruited to the study when it was evident that they had a complete negative work-up and their complaints were compatible with the criteria introduced by Manning (Br Med J 1978; 2: 653). Fasting volumes were twice as large in the IBS (30±3±0 ml) as in the control subjects (15±15±0 ml, p<0.001). Residual volumes were also twice as great in those with IBS compared with the control subjects (12±9±1±8 ml v 5±6±5±8 ml, p<0.01). Increased fasting and residual gall bladder volumes in the IBS are changes that may promote sequestration of cholesterol or calcium salts in the gall bladder of patients with lithogenic bile. Impaired GBC has been previously shown in pregnant women and in people with diabetes, colic disease, post-vagotomy and cystic duct syndrome. In this study GBC is shown for the first time to be impaired in the IBS.

Bile duct diameter after cholecystectomy: assessment by pre and postoperative ERC

S C S CHUNG, J W C LEUNG, S D MOK, and A K C LI (Combined Endoscopy Unit, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong) Whether the common bile duct increase in size after cholecystectomy is controversial. We compared the greatest diameter of the bile duct on endoscopic retrograde cholangiography (ERC) before and 4–12 months after cholecystectomy. One hundred and fifty two patients with uncomplicated gall stone disease underwent pre-operative ERC. Forty three asymptomatic patients agreed to postoperative ERC 139–398 (mean=243) days after cholecystectomy. None had common duct pathology either on pre-operative ERC or at operation. All had cholecystectomy alone. Pre and postoperative ERC of adequate quality were available for scrutiny in 35 patients. The diameter of the common duct was measured at its widest point. Magnification was corrected for by factoring down according to diameter of the endoscope measured on the same radiograph.

The greatest diameter of the common duct measured 0.56–1.58 cm (mean±SD=0.96±0.27) before and 0.73–1.90 cm (mean±SD=1.16±0.29) after cholecystectomy (p<0.00001 Student’s paired t test). The magnitude of dilatation shows a positive correlation with time after surgery (Pearson’s correlation coefficient=0.416, p<0.02).

We conclude that (1) the bile duct on ERC dilates after cholecystectomy, (2) the increase in duct size with time suggests that postoperative dilatation is a physiological phenomenon rather than over distension during ERC.

Urgent endoscopic drainage in acute suppurrative cholangitis

J W C LEUNG, S C S CHUNG, and A K C LI (Combined Endoscopy Unit, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong) Acute suppurrative cholangitis is caused by bacterial infecbion of the biliary tract superimposed upon biliary obstruction, often complicated by septicaemia and shock. The classical treatment is urgent surgical decompression of the biliary tract. Between January 1985 and March 1987, 100 patients (44 men, 56 women; aged 24–95, mean=69 years) with acute cholangitis underwent endoscopic retrograde cholangiography (ERC) during the acute illness (mean interval 1-7 days, range six hours to eight days after admission) with a view to urgent endoscopic drainage. The causes of cholangitis were: common duct stones 85, intrahepatic stones eight, parasites three, malignant obstruction one, uncertain three. Ninety eight per cent of patients had pain, 85% were febrile, 80% were jaundiced. Eighty seven per cent had leucocytosis and 96% had deranged LFTs and 40% were in septic shock. The common duct was successfully cannulated in 98 patients. The biliary tract was drained by sphincterotomy alone (six), insertion of a nasobiliary catheter (26), or both (65). Endoscopic drainage failed in three patients who required emergency surgery and one died. Four died despite successful endoscopic drainage. Endoscopic duct clearance was achieved in 64 patients, while 32 had elective biliary surgery after the cholangitis settled with one death. The overall mortality was 6%.

Urgent endoscopic drainage of the biliary system is indicated in patients with acute suppurrative cholangitis.
Methyl tert-butyl ether for common duct stones: dissolution without radiological appearance

J S DOOLEY, G KAYE, AND J A SUMMERFIELD (Royal Free Hospital, London) Methyl tert-butyl ether (MTBE) dissolves cholesterol gall stones rapidly, but common bile duct stones have resisted dissolution (Gastroenterology 1986; 91: 1296). We have used MTBE given through a nasobiliary or percutaneous transhepatic catheter to treat common bile duct stones (10–40 mm diameter) in four patients (age 43–87 years). Increasing volumes (0.5–6 ml) were flushed in and out every 0.5 to one hour for six hours. The session was terminated if the cumulative loss of MTBE reached 10 ml. Patients received one session a day for up to four days. The maximum volume of MTBE given was 80 ml. There was no change in stone size on cholangiography in any patient. Duct clearance was however achieved in three patients and in two of these, MTBE contributed to the success. In the first, the composition of the stones, as judged by the resistance to basket closure, had changed from rock hard to soft. In the second, mechanical lithotripsy, previously unsuccessful, crushed one of two large stones. The remaining calculus (30 mm) passed spontaneously. In summary MTBE solubilises some common bile duct stones without any change in their cholangiographic appearance. Radiological imaging alone is insufficient evidence on which to conclude that dissolution has failed.

Enterohepatic circulation patterns in man

D L STOKER AND J G WILLIAMS (Royal Naval Hospital, Haslar, Gosport, Hants) No data have been published on variations in the enterohepatic circulation (EHC) in man over 24 hours. This study aims to assess the EHC of bile using a portable gamma probe and SeHCAT. Selected patients (n=8) were given 370 kBq oral SeHCAT. A gamma probe was secured over McBurney’s point (terminal ileum). Counts were recorded every 15 s for 24 h on a Novo Memoral 2A. Results were analysed by computer. There were peaks in counts of two to four times the mean at between one and four hours post-SeHCAT ingestion, and these were followed by further peaks two to four hours later. Further waves then occurred with variable frequency, but of a lower amplitude. In half the patients the counts dropped below the mean and levelled out during sleep, suggesting that bile ceased to circulate, and remained in the gall bladder. In the other half there were continuing large fluctuations in counts overnight, despite the fasting state.

In conclusion, using an external gamma probe and SeHCAT labelled bile, we have shown that bile continues to circulate during sleep in some subjects, while in others it does not. This subject merits further study, as major differences in the enterohepatic circulation may be relevant in a number of disease states such as bile malabsorption diarrhoea and gall stones.

Ursodeoxycholate treatment and postulated mechanism of calcification of previously radiolucent gall stones

J HENDERSON (INTRODUCED BY I W PERCY-ROBB) (Dept of Pathological Biochemistry, Western Infirmary, Glasgow) Medical treatment of radiolucent gall stones is not new. Chenodeoxycholate causes gastrointestinal side effects but not calcification of gall stones; ursodeoxycholate is palatable but causes gallstone calcification after variable periods of treatment, precluding further dissolution therapy. To investigate a possible mechanism for calcification during dissolution therapy we have measured carbon dioxide solubilisation by ursodeoxycholate and chenodeoxycholate solutions using tonometry against 5% CO₂ gas (pCO₂ 35–40 mm Hg). Both bile acid solutions showed increased CO₂ solubility: 113% and 23% respectively for ursodeoxycholate and chenodeoxycholate (both 150 mM) when compared with buffer alone.

We postulate that during administration of ursodeoxycholate, the radiolucent stone is coated with ursodeoxycholate which avidly solubilises CO₂ which will be in equilibrium with HCO₃⁻ and CO₂⁻. CO₂⁻ will form an insoluble precipitate in the presence of Ca²⁺ ions thus causing calcification on the surface. Chenodeoxycholate treatment will coat gall stones with bile acid showing less avid CO₂⁻ solubility and is less likely to act as a source of CO₂⁻.

Long-term results of albendazole therapy of hydatid disease: clinical and experimental results

D L MORRIS, M J CLARKSON, K S RICHARDS, AND D TAYLOR (Department of Surgery, University Hospital, Nottingham) We have previously reported encouraging in vitro, animal model and clinical studies of the use of albendazole in hydatid disease. Long-term results, however, are unknown. Naturally infected Welsh sheep underwent radiology to identify cysts, followed by thoracotomy and needle puncture to confirm viability. Five sheep with live disease received albendazole 10 mg/kg by gavage for six weeks. Instead of immediate necropsy, as in earlier studies, we postponed necropsy for six months to allow any viable material to recover. At necropsy only one of five sheep was found to have viable protoscoleces. Electron microscopy showed complete destruction of the germinal layer in almost all cysts, but some cysts from the single sheep with viable disease had a rela-
Thyroid function as a prognostic indicator in cirrhosis

R P BOLTON, J SHAPIRO, AND M S LOSOWSKY (University Department of Medicine and Biochemistry, St James’s Hospital, Leeds) Various indices of thyroid function, including rT₃, rT₄;T₃ ratio and T₂;T₄ ratio, have been proposed as prognostic indicators in cirrhosis, but none gives a clear cut indication of progress. Using an easily calculated index (Derived Thyroid Index, DTI), based on a single determination of the rT₃;T₄ and T₂;T₄ ratios, we have prospectively evaluated 53 patients with cirrhosis of varied aetiology, following patients until death or for 12 months. Nineteen patients were Child’s grade A, 21 grade B and 13 grade C. Twenty one patients died and a further 14 deteriorated during follow up. The DTI was <2.5 in all 18 patients who remained stable or improved, and was >2.5 in 32 of 35 (91.4%) of patients who died or deteriorated. Of 17 patients with a DTI >3-0, 14 (82.4%) died, whereas six of 15 patients (40%) with a DTI between 2-5 and 3-0 died. Derived Thyroid Index was strongly correlated with disease severity (r=0.703, p<0.001). One patient with a DTI value <2.5 died, and a further two patients deteriorated. Thus, a DTI value of >2.5 gives a sensitivity of 91.4% and specificity of 100% in the prediction of deterioration or death during the following 12 months in patients with cirrhosis, and provides a simple, useful prognostic indicator.

Effect of continued alcohol consumption on bleeding and mortality after variceal haemorrhage

P A MCCORMICK, T YIN, D SPRENGERS, N MCINTIRE, AND A K BURROUGH (Royal Free Hospital School of Medicine, London) Two large studies suggest that abstinence after variceal bleeding in alcoholic cirrhotics does not improve survival and one shows that rebleeding is not affected. We reviewed the subsequent alcohol history and clinical course of 176 consecutive alcoholic cirrhosis after their first admission to the Royal Free Hospital with variceal haemorrhage. Exclusions: died within 30 days, abstinent before bleed six, no follow up four, concomitant other liver disease 6-94 patients were followed up: median 20 months (range 2-97). Drinking was confirmed by history, corroboration from relatives and blood alcohol levels. Thirty remained abstinent and 64 continued to drink. Pugh’s grading at initial presentation and length of follow up were similar in both groups. Mortality was 12/30 (40%) in the abstinent and 23/64 (36%) in the drinkers. Upper gastrointestinal rebleeding (excluding peptic ulcers) occurred in 53% (16/31) of the abstinent v 75% of the drinkers (48/64). There was no significant difference in the rebleeding or mortality rates between the two groups (logrank test), however, there was a trend towards a reduction in rebleeding after eight months of abstinance. Although abstinence probably has a beneficial effect this does not occur early enough to alter the prognosis after variceal bleeding in alcoholic cirrhosis.

Oral urea in the treatment of hyponatraemic ascites

P C HAYES AND ROGER WILLIAMS (Liver Unit, King’s College Hospital, London) The effect of oral urea in patients with cirrhosis and hyponatraemic ascites was studied in 10 patients. Conventional diuretic therapy was discontinued once serum sodium fell below 130 mmol/l and patients randomised to receive three days of oral urea (20 G tid) ‘early’, after the baseline 24 hours, and ‘late’, after a further three days without treatment. Weight fell by a mean of 1.8±2.1 kg (SD) in all patients on urea and this reduction was significantly greater in those randomised to urea early than those receiving no therapy over the first three day period (p=0.04). Serum sodium rose by 4.9±5.3 mmol/l from baseline on urea although the rise was not significantly greater compared with no therapy over three days. Urine output measured over the three day period before and during urea therapy increased from 718±202 ml to 1311±315 ml. Serum urea rose by 14.3±9.6 mmol/l from baseline and was significantly higher compared with no therapy (p=0.03). Serum creatinine fell by 8.2±6.9 μmol/l and urine osmolality increased by 139±145 mmol/l compared with before urea. The serum urea fell rapidly after urea was discontinued.

Diarrhoea and vomiting commonly accompanied urea therapy, requiring a reduction in dosage. Encephalopathy occurred in one patient. Oral urea acts as an osmotic diuretic producing fall in weight and improvement in hyponatraemia but without clinical benefit.

Surgical management of bleeding oesophageal varices: Warren shunt versus lienorenal shunt – 15 years’ experience

J P A LODGE, A I D MAYOR, AND G R GILES (University Department of Surgery, St James’s University Hospital, Leeds) Retrospective analysis of patients undergoing lienorenal shunt (28) or distal splenorenal shunt (36) surgery in 1971-1986 revealed important predictive factors for survival, but showed no significant survival differences between the two shunt groups over a period of up to 14 years.

In 42 patients (64%) active haemorrhage was the reason for operation and 17 of the 18 deaths (22) operative mortality occurred in this group. Patients in whom prolonged conservative resuscitation had been attempted fared worse (64% survival), as did patients with poor hepatic reserve (Pugh grade C: 32% survival). Twenty two patients (27%) rebled within 30 days, 18 after urgent shunts, and 12 died. Seven (11%) of the longterm survivors have suffered recurrent variceal haemorrhage, with a clear relationship to shunt or portal-system thrombosis. Portalasitic encephalopathy occurred in 13 survivors (20%)

We conclude that urgent lienorenal or distal splenorenal shunts for unremitting or relapsing variceal haemorrhage are worthwhile. Selective decompression has been advocated as the procedure of choice, but the non-selective lienorenal shunt is easier to perform and is equally acceptable in terms of postoperative morbidity.

A medical/surgical team approach to the management of acute bleeding varices

D MUTIMER, P D WRIGHT, J FREEMAN, H LOOSE, AND D F W JAMES (Departments of Medicine, Surgery and Radiology, Freeman Hospital, Newcastle upon Tyne) While several controlled trials of different single modalities of treatment for acute bleeding varices have been carried out it seems likely that a treatment plan allowing the use of more
than one method may prove more practical. We have evaluated the use of a ‘multidisciplinary’ treatment algorithm in the management of such patients.

The treatment schedule is centred on early endoscopy (by physician or surgeon on a joint unit), with injection of varices at endoscopy, or insertion of Sengstaken tube with subsequent endoscopic injection within 24 hours. If bleeding persists despite initial injection (or if injection impossible) patients are submitted to gastric devascularisation and oesophageal transection (GDOT) or percutaneous transhepatic embolisation (PTE) the latter for poor prognosis (modified Childs C) patients.

Ninety two patients seen for first time in five years (1982–1986), had 131 emergency admissions with bleeding. Childs grade: 27A, 22B, 43C (37 patients over age 60, 11 under age 20.)

One hundred and thirty one bleeds, one death before treatment. Ninety one controlled with sclerotherapy ± tamponade—84 discharged, seven non-bleeding deaths. Thirty nine continued haemorrhage: 14 no treatment died, 14 GDOT, 11 PTE. Of 14 GDOT bleeding was arrested in 12 (seven discharged). Of 11 PTE bleeding was arrested in nine (seven discharged).

Thus of 131 admissions haemorrhage controlled in 85%, discharge achieved in 75%.

We conclude this ‘team approach’ offers results comparable with the best achieved in ‘single treatment’ centres and in a relatively poor risk group.

Histological improvement after antiviral treatment for chronic hepatitis B virus infection

M G BROOK, I PETROVIC, J A MCDONALD, P JSCHUEER, AND H C THOMAS (Academic Department of Medicine and Department of Histopathology, Royal Free Hospital and Medical School, London) Sequential liver biopsies taken from 50 patients with chronic hepatitis B virus (HBV) infection undergoing therapy with AraAMP or alpha interferons were compared with biopsies from 25 untreated controls. These were scored (1–4) for portal/perportal, lobular and overall inflammation. In those clearing HBe Ag and HBV DNA from their serum, there was a significant reduction in portal/perportal (p<0.01), lobular (p<0.01) and overall (p<0.01) inflammatory activity as compared with controls or non-responders, and none developed cirrhosis. In contrast, inflammatory activity continued in those that did not respond to therapy or received no therapy, and two progressed to cirrhosis. Immuno-cytochemical studies confirmed that in those clearing HBe Ag and HBV DNA from the serum, HBe Ag and HBe Ab were also lost from the liver.

Cirrhosis/fibrosis (p<0.10) and absence of oecin positive hepatocytes (p<0.05) were the only factors to predict response.

The studies support the view that successful treatment of chronic HBV infection is associated with loss of hepatic as well as serum markers of HBV replication and is followed by a reduction in hepatic inflammation, preventing in some cases progression to cirrhosis.

Inflammatory bowel disease posters

Faecal short chain fatty acids (SFA) in ulcerative colitis (UC) and controls

D A BURKE, P G R GODWIN, AND T R AXON (Gastroenterology Unit, the General Infirmary, Leeds and Department of Microbiology, University of Leeds, Leeds) Anaerobes form the bulk of the faecal flora and the SFA are an end product of anaerobic metabolism. Little is known about the anaerobic flora in patients with UC. In vitro work has shown a decreased ability to metabolise SFA by the colonic epithelium. To determine any disturbance in the equilibrium between production of metabolic products and their absorption and metabolism by the colonic epithelium faecal levels of butyric acid (BA) and acetic acid (AA) were measured by head space gas liquid chromatography in 16 patients with UC in relapse and 20 controls and results expressed as μmol/g dry weight. In seven cases SFA were assessed before and after treatment. Colitic faecal BA mean 149 and AA mean 438.5 μmol/g were significantly higher than control BA, mean 28 μmol/g and AA mean 64.5 μmol/g (p<0.005).

There is a significant correlation between BA and AA levels in controls p<0.005 but not in colitics, mean faecal BA and AA before and after treatment were 126 μmol BA/g, 187.5 μmol BA/g and 368.5 μmol AA/g, 550 μmol AA/g respectively (NS).

This study shows that faecal SFA in patients with UC are significantly raised and suggests either over production or decreased utilisation of these fatty acids. These data support the in vitro studies showing impaired metabolism of SFA in UC.

Inhibition of fatty acid oxidation as a cause of ulcerative colitis

W E ROEDIGER AND S H NANCE (INTRODUCED BY S C TRUELOVE) (Department of Surgery and Cell Physiology Laboratory, University of Adelaide at The Queen Elizabeth Hospital, Adelaide, Australia) Studies have shown that ulcerative colitis is associated with inhibition of fatty acid oxidation in colonocytes and that inhibitors of fatty acid oxidation induced colitis in experimental animals. The hypothesis was tested whether a weak inhibitor of fatty acid oxidation (2-bromobutyrate, 4-mercaptopbutyrate) in conjunction with a selective stimulator of fatty acid oxidation (sodium nitrite) could reproduce strong inhibition of fatty acid oxidation in colonocytes similar to the biochemical lesion observed in human colitis. Isolated colonocytes of the rat were used to measure fatty acid oxidation as 14C02 production from [1-14C] butyrate. 4-Mercaptopbutyrate alone inhibited 14C02 production by 2.40% and 2-bromobutyrate alone inhibited 31.4±1.3% of fatty acid oxidation. Combination of bromobutyrate and sodium nitrite inhibited 73±2.8% of fatty acid oxidation. Bromobutyrate inhibited ketogenesis by 42±4% which was doubled (89±3±6±5%) in the presence of sodium nitrite. The proposed hypothesis was upheld from which it is suggested that an inhibitor of fatty acid oxidation from the colonic lumen in conjunction with a stimulator of fatty acid oxidation, nitrite, known to be generated from laminal cells are needed to produce the biochemical lesion observed in human ulcerative colitis.

Milk antibodies and circulating immune complexes in inflammatory bowel disease

J MAIN, H MCKENZIE, C R PENNINGTON, AND D PARRATT (Department of Medical Microbiology, Ninewells Hospital and the Department of Medicine, Kings Cross Hospital, Dundee) IgG and IgA antibodies against whole milk and certain milk antigens were estimated by an ELISA in 44 patients with Crohn’s disease, 42 patients with ulcerative colitis and a control group (25). IgG and IgA containing circulating immune complexes (CIC) were estimated by a conglutinin binding ELISA. Anticasein IgA antibodies were significantly elevated in both disease groups (p=0.05, Mann-Whitney). IgG and IgA containing CIC were significantly elevated (p<0.05, Mann-Whitney) in the Crohn’s disease (IgG mean=374 μg/ml, range 0–3000; IgA
mean = 47 µg/ml, range 0–1000) and ulcerative colitis (IgG mean = 192 µg/ml, range 0–3000; IgA mean = 42 µg/ml, range 0–660) groups when compared with controls (IgG mean = 83 µg/ml, range 33–210; IgA mean = 8 µg/ml, range 0–75). There was a significant correlation between milk antibody and CIC values for IgG in Crohn’s disease (r = 0.78, p < 0.01) but not in ulcerative colitis (r = 0.28, p > 0.05). The correlation between milk antibody and CIC values for IgA was significant for both Crohn’s disease (r = 0.82, p < 0.01) and ulcerative colitis (r = 0.54, p < 0.01).

The observed correlation between CIC and food antibody supports the possible association between CIC and food antigen processing. In inflammatory bowel disease increased absorption of food antigens may generate high levels of CIC, although their pathogenetic significance remains uncertain.

Colonic lymphoid subpopulations in inflammatory bowel disease
M C ALLISON, I. W POULTER, A. P DIHILLON, AND R E POUNDER (Royal Free Hospital, London)

Although lymphocytic infiltration is a well-known feature of ulcerative colitis (UC) and Crohn’s colitis (CC), the location of T and B cell subtypes and their state of activation have not been fully characterised immunohistologically. Frozen sections of colonic biopsies or resections from five patients with active UC, 13 with Crohn’s disease (five with colitis) and seven controls were stained with a panel of monoclonal antibodies using an immunoperoxidase technique. The antibodies were RFT Mix (recognising T cells), RFB Mix (B cells), Leu 3A (helper T cells), SN 130 (subsets of T and B cells) and anti Tac (a marker of T cell activation). The histologically normal sections and those from patients with CC displayed marker variations in mucosal T cell populations that did not correlate with disease activity. However enhanced basal lymphoid aggregates with wide submucosal extension were found in all CC sections, and these aggregates contained many Tac positive cells. By contrast, marked mucosal infiltration with all T cell subtypes, including many Tac positive cells, was found in the UC sections. B cells were present in lymphoid aggregates but not in the mucosal infiltrate.

These observations offer evidence that the immunopathogenesis of UC and CC both involves a cell-mediated immune response but show marked differences in cellular localisation.

Macrophage and lymphoid subpopulations in the granulomata of Crohn’s disease
Y R MAHIDA, S PATEL, K WU, AND D P JEWELL (Gastroenterology Unit, Radcliffe Infirmary, Oxford) Granulomata are a characteristic feature of Crohn’s disease. This study describes the distribution of macrophage and lymphocyte subpopulations in the granulomata of four patients with Crohn’s disease (three ileal, one colonic).

Tissue was snap frozen and 4 µ sections stained using the peroxidase and alkaline phosphatase techniques, singly or in combination. Acid phosphatase (ACP) and non-specific esterase (NSE) staining was also performed. Monoclonal antibodies used: RFD1 (interdigitating cells), RFD9 (epithelioid cells and tingible body macrophages). RFD7, EB11 (tissue macrophages), 3C10, Y1/82A, UCHM1 (monocytes and macrophages), 3G8 (Fcγ receptor on polymorphs and some macrophages), CR3/43 (HLA-DR), BT3/4 (HLA-DQ), IL2R (interleukin 2 receptor), T310 (CD4), DK25 (CD8).

The epithelioid cells and giant cells were strongly RFD1+, RFD9+, EB11+, 3C10+, Y1/82A+, CR3/43+, BT3/4+, ACP+, NSE+, and moderately 3G8+, UCHM1+ and IL2R+. RFD7+ cells (weakly ACP+, NSE+) only occurred at the periphery of the granuloma. Lymphocytes within the granulomata were mainly CD4+ CD8+ cells were few and scattered mainly at the periphery in association with RFD7+ macrophages. This distribution is in contrast with that seen in chronic intestinal granulomatous disease.

Crohn’s granulomata comprise epithelioid cells (RFD9+, RFD7+) intimately associated with CD4+ lymphocytes. Epithelioid cells are IL2R+ and appear to be activated.

Mucosal glycoprotein synthetase in Crohn’s disease: a protective mechanism?
M C WINSLET, VALERIE POXON, A ALAN, AND M R B KUGHLEY (The General Hospital, Birmingham) Glucosamine synthetase (GS) in mucosal glycoprotein synthesis. Increased rectal GS activity has been reported in patients with ileal Crohn’s disease (ICD) which may represent a protective response to toxic luminal factors. To test this hypothesis, rectal GS activity was measured in ICD (n = 11). Crohn’s proctitis (CP, n = 11) and a control group (n = 11) before and two, six, and 12 weeks after a defunctioning ileostomy. The effect of restoration of intestinal continuity was also assessed in Crohn’s disease (CD, n = 9) and controls (n = 7). Predulence GS activity was significantly increased in the ICD group compared with controls (34±8±4, 22±9±3, 4, p < 0.05). Postdefunction – there was no change in GS activity in the control group but ICD activity had fallen significantly from 34±8±4 to 19±2±3 at six weeks, and 16±4±2±5 at 12 weeks, p < 0.01. Crohn’s proctitis activity had fallen significantly from 28±6±3 to 16±2±2±5 at six weeks, p < 0.01. On restoration of intestinal continuity, there was a significant increase in CD from 14±7±2±5 pre-operatively to 25±5±3±7 at two weeks, p < 0.01 but no change in the control group. These results suggest that a luminal factor significantly stimulates glycoprotein synthesis in Crohn’s disease. This finding supports the role of a toxic facetal component stream in the pathogenesis of Crohn’s disease.

Personality in inflammatory bowel disease (IBD): primary, or secondary to chronic illness?
D A F ROBERTSON, J RAY, AND I DIAMOND (Departments of Medicine and Social Statistics, University of Southampton, Southampton) The high prevalence of personality traits of neuroticism, anxiety and introversion is well described in IBD, but whether these are secondary to disease, or a primary phenomenon, is unknown. We have measured the Hospital Anxiety and Depression scale (HAD) and Eysenck personality inventory (EPI) measuring neuroticism and extraversion on a linear scale (1–24) in 80 IBD patients, in 22 newly referred patients before the diagnosis of IBD, and in 40 controls (Diabetics attending a clinic). Inflammatory bowel disease patients were more neurotic (mean EPI 12±0 v 9, p < 0.05) and less extraverted (9±8 v 12±0, p < 0.05) than controls and these traits are present before diagnosis (EPI neuroticism 13±9 v 12, EPI extraversion 9±8 v 9±8, NS). In established disease, depression correlates strongly with disease activity and introversion with disease duration. Patients were aware of a close link between stress and disease activity: 59 identified a stressful life event which they believed precipitated the illness. Neuroticism and introversion are common in IBD patients and these traits are present before diagnosis. Depression occurs predominantly in those with active disease, and introversion increases as the disease progresses.
Smoking and sugar intake are separate but interactive risk factors in Crohn’s disease

R KATSCHINSKI, R F A LOGAN, M EDMOND, AND M J S LANGMAN (Departments of Therapeutics and Community Medicine and Epidemiology University of Nottingham, Nottingham) Previous studies have consistently found a strong positive association between sugar intake and Crohn’s disease (CD) and recently others have found a strong association between smoking and CD. As sugar intake and smoking are often linked we have investigated this relationship in 104 CD patients and 153 matched community controls. Data on added sugar intake (AS), confectionery consumption and smoking habits were obtained by postal questionnaire. Relative risk (RR) estimates (95% confidence limits) were derived using Mantel-Haenszel analysis. Added sugar intake and smoking were associated with one another. After adjusting for AS smoking still showed a significant association with CD with a RR of 1.8 (1.04–3.2). Equally after adjusting for smoking AS was also strongly associated with CD in a dose-response pattern (χ²=7.7; p<0.025) but this relationship was only evident in never and ex-smokers. For never and ex-smokers the RR’s associated with no AS, ≤50 g/day and >50 g/day were respectively 1.0, 1.8 (0.8–3.0) and 4.6 (2.0–11) (χ²=12.1; p<0.005) and for smokers 1.0, 0.8 (0.2–2.7), 1.1 (0.4–3.1) respectively. The AS relationship was supported by a separate association with confectionery consumption with the RR’s of never or < monthly consumption, monthly, and weekly or more often being respectively 1.0, 1.7 (0.7–4.0) and 3.0 (1.2–7.5) (χ²=6.8; p<0.005). These findings indicate that while smoking and AS are individually associated with CD combined exposure results in no further increase in risk, suggesting that they may operate through a common mechanism.

Are clinical activity indices helpful in assessing active intestinal inflammation in Crohn’s disease?

G E CRAAMA-BOBHOUTH, J BIELMONT, A S PENA, H W VERSPAGT, I T WETTERMAN, AND C B W LAMERS (Dept Gastroenterology and Hepatology, University Hospital Leiden, The Netherlands) Quantification of the faecal excretion (FE) of iv administered autologous Indium-111 tropolone labelled granulocytes is a reliable parameter of bowel inflammation. In this study we correlated 24 h Indium-111 FE with several clinical activity indices for Crohn’s disease (CD) such as CDAI (Best et al), AI (van Hees), SI (Harvey and Bradshaw), Oxford Score, and laboratory parameters: ESR, serum albumin, osmornocid, C-reactive protein, α1-antitrypsin (α1-AT) faecal concentration, and α1-AT clearance. Twenty eight CD patients (18 F, age 16–60 years) were studied. Nine had colonic involvement, 18 had small bowel localisation, one patient colonic and small bowel involve-ment. Indium-111 activity of faeces samples were measured in a gamma counter and expressed as per cent of the injected dose. The median was 8% (range 0.15–50%) for colonic involvement and 0–75% (range 0.03–2.1%) for small bowel disease.

No significant correlation was found between Indium-111 FE and any of the four activity indices used in this study, neither for colonic nor for small intestine or both combined. Indium-111 FE however was positively correlated with osmornocid (r=0.53; p<0.05), α1-AT faecal concentration (r=0.64; p<0.05), α1-AT clearance (r=0.39; p<0.05), and negatively correlated with serum albumin (r=−0.52; p<0.05).

None of the studied activity indices reflect accurately the degree of inflammation as assessed by Indium-111 FE. Objective laboratory parameters should be used in studying activity of CD. Indium-111 FE is therefore a good parameter which can be used in the evaluation of new forms of treatment.

Observer variation in the histopathological assessment of rectal and colonic biopsies

A THEODOSII, D J SPIEGELHALTER, J JASS, J FIRTH, M DIXON, M LEADER, D LEVISON, R LINDLEY, I FILIPE, A PRICE, N A SHEPHERD, S THOMAS, AND H THOMPSON (The Mayday Hospital, MRC Biostatistics Unit Cambridge, Departments of Pathology, St Marks, Westminster, St Batholomews, Guys, Northwick Park Hospitals, Leeds, General Infirmary, and The General Hospital, Birmingham) If skilled histopathologists disagree over the interpretation of the same biopsy this leads to diagnostic error. The aim of the present study was to determine the magnitude of variation amongst ten observers with a special interest in gastrointestinal histopathology, who independently interpreted the same biopsies for morphological features which may discriminate between patients with Crohn’s disease (n=24), ulcerative colitis (34), and normal subjects (18). More than 50,000 items of information were evaluated.

Although 38 of 51 features had agreement measures significantly better than expected by chance, only three (neutrophil infiltration of crypt epithelium, neutrophils in lamina propria and Langhans giant cells) had Kappa values of 0.4 or greater, such values being considered to show fair to good agreement. Thus, the vast majority of features had Kappa values indicating poor agreement beyond chance. The range of agreement amongst the 45 observer pairs over the final diagnosis was 65–76%. Only normal biopsies had a Kappa value greater than 0.4. Those from patients with ulcerative colitis and Crohn’s had Kappa values of 0.3 and 0.2 respectively.

These results suggest that there is considerable room for improvement in the reliability of colonic biopsy interpretation and could probably be achieved using more exact definitions of morphological features and diseases.

Tc-99m-HMPAO labelled white cell imaging – a new technique for the dynamic assessment of inflammatory bowel disease

A H M HEAGERTY, D C COSTA, D LUI, J M F CLARKE, S R CAIRNS, P J ELLI, AND N I MCMENIH. (Department of Gastroenterology and Institute of Nuclear Medicine, Middlesex Hospital, London) The assessment of activity and extent of inflammatory bowel disease (IBD) by endoscopy or radiology is time-consuming, uncomfortable, often technically difficult and open to misinterpretation. Using tracer labelled white cells for dynamic imaging to assess the extent of inflammation has much improved the situation.

Tc-99m-Hexamethylpropylenemacoinoxime (Tc-99m-HMPAO) has been identified as a useful tracer for white cells. This was simultaneously compared with the established Indium-111 oxide (In-111) labelling technique in 12 patients with known or suspected IBD at one, four, and 20 h using appropriate energy windows for the isotopes. One patient had scans seven days before, and 60 days after resection of ileal Crohn’s disease as well as imaging of the resected specimen.

This study showed that both isotopes produce identical leucocyte distributions in these patients, ranging from nothing to extensive intestinal uptake in small bowel Crohn’s disease. The resolution with Tc-99m-HMPAO was uniformly better than with In-111. Scans of the operative specimen showed localisation specific to the active disease.
Assessing the extent of IBD with Tc-99m-HMPAO labelled white cells has the principal advantage of better resolution without missing active disease and utilising a more readily available tracer. We believe it is the standard isotopic method of choice in assessing IBD, until an in vivo labelling technique is widely available.

Effects of prednisolone, sulphasalazine, 5-aminosalicylic acid and indomethacin on prostaglandin E2 and leucotriene B4 production

J J Keating, W J Maxwell, F P Hogan, and P W N Keeling (Dept of Clinical Medicine, Sir Patrick Dun Research Laboratory, St James’ Hospital, Dublin) Sulphasalazine (S/S) and 5-aminosalicyclic acid (5-ASA) decreases the frequency of relapse, whilst prednisolone (Pred) controls the acute inflammatory response in patients with inflammatory bowel disease (IBD). The aims of our study were to compare the in vitro effects of S/S, 5-ASA, Pred and indomethacin (INDO) on eicosanoid [prostaglandin E2 (PGE2) and leucotriene B4 (LTB4)] biosynthesis by stimulated peripheral blood mononuclear cells from patients with IBD. Cells were stimulated with opsonised zymosan and PGE2 and LTB4 biosynthesis assessed by radioimmunoassay. Indomethacin and Pred inhibited PGE2 production (3-3±0.2, n=6 v 8-0±1.8, n=7 v 15-4±3, n=7, p<0.05 ng PGE2/10^6 monocytes, INDO v Pred v control). Neither drug significantly altered LTB4 production. In contrast S/S and 5-ASA increased PGE2 concentration (44-6±11-6, n=7, 48-5±10-8, n=7 v 15-4±3, n=7, p<0.025, cells cultured with S/S v 5-ASA v control cells). Again neither drug significantly altered LTB4 production. The results suggest that pharmacological manipulation of PGE2 and LTB4 biosynthesis may play a different role in the management of acute and chronic IBD hence Pred decreases PGE2 production during an acute episode and may decrease the inflammatory reaction whilst S/S and 5-ASA increase its synthesis and hence modulate the chronic immune response.

Oral tobramycin improves the outcome of acute ulcerative colitis (UC)

D A Burke, S A Clayden, M F Dixon, A T R Axon, and R W Lacey (Gastroenterology Unit, The General Infirmary, Leeds and Department of Microbiology and Depart-ment of Pathology, University of Leeds, Leeds) Patients with UC harbour adhesive E. coli in their colon. This double blind trial was performed to determine whether eradication of E. coli is of benefit. Eighty four patients with UC in relapse were randomised to seven days tobramycin (T) 120 mg tds or placebo (P) as an adjunct to steroid treatment. Patients were assessed by clinical and histological scoring at entry and endpoint (EP) (21 days for inpatients, 28 days for outpatients). Culture for faecal E. coli was undertaken at entry, seven days and EP. Tobramycin and P groups were well matched for age, sex, extent of disease, length of history and duration of relapse. Bacteriologic results were unsuitable for analysis in 6 T and 7 P. In the remainder seven day assessment showed that E. coli had been eradicated in 77% T and 8-8% P, p<0.0001 and the strain changed by EP in 91% T and 13-8% P, p<0.0001. From each group one patient went to surgery and one failed to attend during the trial. Clinical and histological scores in each group were similar at entry but at EP were significantly lower in the T group (p=0.04 and 0.03 respectively). Complete symptomatic remission was obtained in 3/42 of T and 18/42 P, p=0.008. Ten of 10 first attacks in T and 6/10 in P achieved remission by EP (p=0.04). Oral tobramycin successfully eradicates the original E. coli strain in at least 77% of patients with UC and is associated with a significant clinical and histological benefit.

A comparison of delayed-release 5-aminosalicylic acid (5-ASA) and sulphasalazine (SSZ) as maintenance treatment of ulcerative colitis (UC)

S A Riley, V Mani, M J Goodman, and L A Turnberg (University Dept of Medicine, Hope Hospital, Salford, Leigh Infirmary, and Bury General Hospital, Manchester) Many patients with UC are denied the beneficial effects of SSZ as side effects are common. As most of these are related to the sulphapyridine component of the drug we have assessed the efficacy of a delayed-release 5-ASA preparation in maintaining UC remission.

One hundred patients (51 M:49 F, aged 20–78 years) with quiescent UC were randomly allocated to either enteric coated SSZ or equivalent dose 5-ASA in a double-blind 48 week trial. Eight patients were withdrawn (four non-attendance, two non-compliance, one stomatitis (SSZ), and one inappropriate inclusion) leaving 44 SSZ and 48 5-ASA for analysis. Groups were comparable for age, sex, duration, and extent of disease.

Relapse rates at 48 weeks were SSZ 38-6% (95% confidence limits 24–54%) and 5-ASA 37-5% (95% confidence limits 24–53%) p=0.01. p>0.90. Mean time to relapse and relapse severity were similar in the two groups. Headaches and upper gastrointestinal symptoms were less common in the 5-ASA than in the SSZ group. Haemoglobin concentration rose and MCV fell during 5-ASA treatment. Folate levels, however, remained unchanged.

Delayed release 5-ASA is as effective as SSZ in maintaining UC remission and has fewer side effects.

Combination antimycobacterial chemotherapy with major clinical response in established Crohn’s disease

M Parker, S Hampson, S Saverymuttu, S Cawthorn, J J Mckadden, J Thompson, E Green, K Rutter, and J Hermon-Taylor (Department of Surgery, St George’s Hospital Medical School, Cranmer Terrace, London) Some Crohn’s disease (CD) mycobacterial isolates have been shown to be indistinguishable from M. paratuberculosis on the basis of restriction fragment length polymorphisms using cloned mycobacterial DNA probes. Seventeen patients with established Crohn’s disease were treated with rifampicin, isoniazid, ethambutol and pyrazinamide for up to nine months. Disease was assessed by CD activity index (CAI) monthly, and by Indium scanning, colonoscopy, histology and radiology before, three and nine months after treatment. Three patients have not yet completed initial assessment. Treatment failed in two patients because of non-compliance although one of these had responded before withdrawal. Eleven of 12 patients responded, mean initial CAI of 275±99-7 (ISD) falling to 176±93 within one month. In five patients with severe intractable CD refractory to conventional therapy, response was dramatic and impending surgery was avoided. Although disease course after cessation of chemotherapy is not yet known, these early results would support a wider study of this approach in the clinical management of CD.

The British Society of Gastroenterology
Fish oil for inflammatory bowel disease?

J P RICHARD, T K DANESHMEND, J E WILLARS, B FILOPOWICZ, D LESTER-SMITH, AND C J HAWKEY (Departments of Therapeutics, University Hospital, Nottingham) Leucotrienes synthesised from the precursor eicosapentaenoic acid (EPA) - that is, LT5B, appear to be less pro-inflammatory than those derived from arachidonic acid - that is, LTB4. Administration of fish or fish oil high in EPA may thus be beneficial in inflammatory conditions such as ulcerative colitis. We have investigated the biochemical consequences, safety and efficacy of this dietary approach. Consumption of fish oil (Hi-EPA, 20 ml/day, giving 4 grams of EPA per day) for one month caused an increase in cell membrane EPA from 1.7±0.16% (mean ±SE) to 3.35±0.34% of total fatty acids (GC assay), a 55% (95% confidence limits: 40–70%) decrease in the detectable amount of the pro-inflammatory compound LTB4 (HPLC assay). Production of the less inflammatory compound LT5B was detectable in only four of 12 subjects under control conditions, but was present in eight subjects after fish oil. In an open pilot study, five subjects with severe colitis resistant to steroids were treated with the addition of Hi-EPA, 20 ml/day, and azathioprine (2 mg/kg/day) to existing therapy. After three to four weeks, all had improved and four were in remission. Fish oil caused no significant adverse effects and its use in inflammatory bowel disease warrants further investigation.

Controlled trial of clofazimine in Crohn’s disease

N H AFDHAL, A LONG, J LENNON, J CROWE, AND D P O’DONOGHUE (Dept of Gastroenterology, St Vincent’s and Mater Misericordiae Hospitals, University College, Dublin, Ireland) The aetiology of Crohn’s disease remains obscure and an infective agent, perhaps an atypical mycobacterium, has been proposed. A preliminary study with clofazimine (CL), a broad spectrum anti-mycobacterial agent with both anti-inflammatory and neutrophil stimulating properties, was favourable but has remained unconfirmed (Gut 1982; 23: 449). Therefore to determine the effect of CL on inducing disease remission, 49 patients (34 F, age 28±13 years) with active Crohn’s disease were randomised to receive corticosteroids and either CL 100 mg (25) or matching placebo (PL, 24). Disease activity was monitored using a modified disease activity score (DAS) combining subjective symptoms with changes in haemoglobin, ESR and serum albumin. Remission was defined as reduction in DAS≤4, and steroid withdrawal within three months with no evidence of relapse for a further month. At randomisation (induction phase) both groups were similar for site of disease (large bowel 25, small bowel 24), number of previous relapses, median DAS (CL 10, PL 9–5) and median initial steroid dosage (45 mg). Twenty seven patients (55%) achieved remission (median DAS: 1) and there was no difference between the two groups (CL 15: PL 12, p=NS). In the second phase of the study (maintenance phase) these 27 patients continued to receive either CL or placebo for a further 8 months or until relapse, defined as an increase in DAS≥8. Eighteen patients (38%) had no further relapse (CL 12: PL 6, p=NS) and successfully completed the trial. Side effects were minor and consisted of skin rash (CL 3) and increased pigmentation (CL 12, PL 5).

In conclusion, clofazimine was neither effective in inducing or maintaining remission and is further indirect evidence against a mycobacterial aetiology for Crohn’s disease.

An audit of the management of Crohn’s colitis

H A ANDREWS, P LEWIS, J ALEXANDER-WILLIAMS, M R B KEIGHLEY, R N ALLAN, AND J ALEXANDER-WILLIAMS (Gastroenterology Unit, General Hospital, Steelhouse Lane, Birmingham) It is now clear that limited resection is appropriate for small bowel Crohn’s disease particularly as the risk of re-operation is not affected by histological evidence of involvement at the resection margins. This study evaluates the place of limited resection in colonic disease.

Thirty six patients underwent segmental colonic resection for Crohn’s colitis between 1944 and 1986. None of the 29 patients undergoing segmental resection and primary anastomosis had anastomotic dehiscence. There were two postoperative deaths from septicaemia in elderly patients. At 10 years the cumulative re-operation rate was 60% compared with 48% after colectomy and ileorectal anastomosis, and 24% after panproctocolectomy. There was a significantly higher recurrence rate in the segmental colectomy group (x2 p<0.006) compared with the recurrence free interval curves following total colectomy with ileorectal anastomosis or panproctocolectomy.

There was no apparent functional or nutritional advantage from retaining residual functioning colon following local colonic resection. We now rarely recommend segmental colectomy for colonic Crohn’s disease.

Sustained epithelial proliferation after faecal diversion for Crohn’s disease objective evidence of mucosal recovery

Extensive colonic disease (n=145): 22% were treated conservatively. Of those undergoing resection (mean interval 6-7 years) the cum-re-op was 48%, 61%, and 79% at 5, 10, and 15 years. Currently 92% of survivors are well although 45 (41%) have evidence of recurrent disease and 78 (67%) have a permanent stoma. Only nine patients are symptomatic. In total there were 36 related and 24 unrelated deaths. The commonest causes of related death were sepsis (16), electrolyte imbalance (seven), and cancer (six).

The longterm prognosis is good even though the incidence of reoperation for recurrent disease is high. Most patients are currently well although many have to accept a permanent stoma to achieve this status.

Segmental colectomy for Crohn’s disease of the colon

H A ANDREWS, A ALLAN, C J HILTON, M R B KEIGHLEY, R N ALLAN, AND J ALEXANDER-WILLIAMS (Gastroenterology Unit, General Hospital, Steelhouse Lane, Birmingham) It is now clear that limited resection is appropriate for small bowel Crohn’s disease particularly as the risk of re-operation is not affected by histological evidence of involvement at the resection margins. This study evaluates the place of limited resection in colonic disease.

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Sustained epithelial proliferation after faecal diversion for Crohn’s disease objective evidence of mucosal recovery
Entero vaginal fistulae in Crohn's disease

FRANCOISE HENY, M WINSLET, H ANDREWS, R N ALAN, M R B KEIGHLY, AND J ALEXANDER-WILLIAMS (The General Hospital, Birmingham) Conservative management of entero vaginal fistulae in Crohn's disease has been advocated for less symptomatic patients. We reviewed 27 patients with spontaneous entero vaginal fistul e complicating active disease, seen between 1970 and 1987. Ten required early operation, including three proctectomies. Conservative management healed no fistula in 16 patients. During this long follow up (two months to 35 years), six patients required a panproctocolectomy; one patient had a total colectomy for megacolon and one had a defunctioning stoma for stricture. Two symptomatic patients died of unrelated causes, four are still mildly symptomatic. Two patients died of malignancy arising from within the chronic enterovaginal fistula. Although some enterovaginal fistulae cause little local disability and can be managed symptomatically by scrupulous hygiene, they do not heal on conservative measures and in time the majority develop such severe bowel symptoms that resection, usually proctectomy, is required. As two patients in this group developed cancer in the fistula track, we would now recommend early consideration of radical surgical therapy for enterovaginal fistulae in Crohn's disease.

Enterovaginal fistulae in Crohn's disease

M C WINSLET, DENISE YOUNGS, A ALAN, AND M R B KEIGHLEY (The General Hospital, Birmingham) Faecal diversion for Crohn's colitis frequently produces clinical remission but there is no objective evidence of mucosal recovery. The effect of faecal diversion may be mediated by changes in mucosal cellular kinetics. To test this hypothesis, the cell birth rate (crypt cell production rate - CCPR) of rectal mucosa in patients with ileal Crohn's disease (ICD, n=11). Crohn's proctitis (CP, n=9) and a control group (n=10) was measured before and two, six, and 12 weeks after a defunctioning ileostomy. Crypt cell production rate was assessed by an in vitro stathmosis kinetic method. There was no significant difference in pre-diversion levels of CCPR (control=3.4±1.0, ICD=2.8±0.6, CP=2.4±0.9). Post-diversion there was a significant reduction in the CCPR of the control group at two weeks (1.2±0.4, p<0.05) but not at six weeks (1.7±0.4) or at 12 weeks (3.3±1.5). There was no significant change in CCPR of the ICD or CP group at two weeks (ICD=2.0±0.7; CP=3.0±0.8), six weeks (ICD=2.1±0.8; CP=3.8±1.4) or 12 weeks (ICD=2.1±0.5; CP=2.1±1.6). The sustained proliferation rate after diversion in Crohn's disease compared with the significant fall in the control group may represent a regenerative mechanism promoting epithelial repair. This response suggests that a toxic faecal component may perpetuate the inflammatory process in Crohn's disease.

Detection of asymptomatic inflammatory bowel disease while screening for colorectal cancer

K C BALLANTYNE, J F MAYBURY, G PYLE, C MANGHAM, AND D J HARDCASTLE (Department of Surgery, University Hospital, Nottingham) Previous studies based on hospital diagnosis of symptomatic patients have estimated the prevalence of inflammatory bowel disease (IBD) to be between 80-150/100,000. In Nottingham the existence of a screening programme for colorectal cancer has provided an opportunity for the detection of apparently asymptomatic cases of IBD and the prevalence to be assessed.

Between 1983 and 1987, 37,000 individuals aged 50-75 years have been offered faecal occult blood tests (FOBT), either three or six day Haemoccult or Feca ELA, as a screening test for colorectal neoplasia. Seventeen thousand nine hundred and thirty individuals have completed the FOBT's and of these 481 have been positive. Colonic investigation in these individuals revealed eight patients with previously undiagnosed IBD: five patients had total ulcerative colitis, one proctitis, and two Crohn's disease. Two further patients with ulcerative colitis were identified who had been lost to follow up for 25 and 45 years respectively. The prevalence of ulcerative colitis in this population was at least 44/100,000 (95% CI 11.2-78.1) while that of Crohn's disease was 11.2/100,000 (95% CI 0.4-48.6). Thus the combined prevalence of IBD was 56/100,000 and this data suggests that current epidemiological studies underestimate the UK prevalence of IBD by at least 30%.

BASIC SCIENCE

Coeliac sprue (CS): the sequence of immunopathological events after rectal gluten challenge

D E Loft, P T CROWE, AND M N MARSH (Department of Medicine, Hope Hospital, Salford, Manchester) To document the changes in rectal mucosal structure, epithelial lymphocyte populations and mast cells following local gluten challenge in CS patients and controls (C).

Biopsies were taken pre- and at 1, 2, 4, 6, 8, 12, 14, 16, 36, 48, 60, 72, 96 hours post-challenge, with either 2 g FF3 (n=9 CS/6 C) or 500 mg B lactoglobulin (n=6 CS/6 C) instilled rectally. Each biopsy was quantified by computerised image analysis for: (1) lamina propria volume (LPV), surface, and crypt epithelial volumes; (2) absolute crypt, epithelial lymphocyte population (CEL), and (3) Epithelial lymphocytes were phenotyped with monoclonal antibodies. (4)
vascular permeability monitored with peroxidase-anti-fibrinogen antibody and (5) mast cell structure assessed by EM.

There was a marked rise in OKT8+ suppressor-cytolytic CEL maximal at six hours (115% increase) in CS (p<0.01). Lamina propria volume increased at one hour and significantly so by six hours (p<0.05) reflecting mucosal oedema due to microvascular extravasation, as shown by extensive fibrinogen deposition within the lamina propria one hour postchallenge. There was no EM evidence of mast cell discharge. There was no response to β-lactoglobulin in CS or C.

In CS, rectal gluten instillation: (1) causes a rise in OKT8+ CEL maximal at six hours; (2) evokes an early increase in microvascular permeability and tissue swelling that is not mast cell mediated or due to the later lymphocytic infiltrate.

Synergism of hepatotropin, a novel hepatotropic factor, and insulin on DNA in rat hepatocytes

C SELDEN AND H J F HODGSON (Dept of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London)

Liver regeneration can be modulated by glucagon, insulin and epidermal growth factor (EGF). We report the in vitro hepatotropic activity of a high molecular weight fraction of human and rat serum after partial hepatectomy, and identified the factor in rats as a protein of subunit molecular weight approximately 100000 daltons on SDS-PAGE. In this study we tested hepatotropin in hepatocyte cultures with glucagon, insulin and EGF. There was a purely additive effect on DNA synthesis when hepatotropin was added to glucagon and EGF, but a striking synergistic effect on DNA synthesis when hepatotropin was added with insulin. 91-Thymidine incorporation in the presence of insulin alone was 21 100, 16 840, and 11 740 dpm/20000 cells (10 \(^{-9}\), \(10^{-8}\), and \(10^{-7}\) M insulin); hepatotropin was 28 632 dpm/20000 cells. Thymidine incorporation at the same concentration of hepatotropin with insulin was 58 552, 61 428, and 59 008 dpm/20000 cells at the three insulin concentrations. (Quadruplicate cultures in three separate experiments.

This striking synergism between insulin and hepatotropin requires further investigation. Possibilities include positive cooperativity between the membrane receptors, as occurs between insulin and somatotemedin, or the activation of different intracellular second-messengers.

Different effects of VIP and PHI on intestinal adenylate

J A SMITH AND R G LONG (Medical Research Centre, City Hospital, Nottingham) Vasooactive intestinal peptide (VIP) and peptide histidine isoleucine (PHI) are closely related regulatory peptides. Vasoadactive intestinal peptide is an intestinal secretagogue that exerts its effect by increasing intracellular cAMP levels. The adenylate cyclase of intestinal epithelial cells appears to have receptors specifically for VIP but not for PHI. Peptide histidine isoleucine has been reported to have an affinity for VIP receptors. Fluoride ions are used to stimulate adenylate cyclase activity in a nonspecific way via guanine nucleotide binding N proteins.

The effect of VIP and PHI on basal and fluoride stimulated adenylate cyclase was assessed in homogenates of normal human duodenal biopsies. Results are expressed as mean±SEM pmol cAMP/minute/mg protein. VIP (10 \(^{-8}\) M to 10 \(^{-4}\) M) and PHI (10 \(^{-6}\) M to 10 \(^{-4}\) M) stimulated basal adenylate cyclase. Maximal stimulation of basal adenylate cyclase (10.5±3.22) was achieved with VIP (19±5±7.39) and PHI (22.28±6.43) at a concentration of 10 \(^{-6}\) M. Both VIP and PHI were inhibitory at 10 \(^{-5}\) M. In the presence of 10 mM sodium fluoride PHI failed to stimulate further whereas VIP continued to stimulate adenylate cyclase in a linear manner. Thus in vitro PHI may stimulate adenylate cyclase in a different way to VIP.

Endocrine tumours in ARG-vasopressin/simian virus 40 large T antigen transgenic mice: a model for human multiple endocrine neoplasia type I syndrome

A E BISHOP, G RINDI, D MURPHY, J HANSON, G W H STAMP, M MURPHY, B HOGAN, AND J M POLAK (Depts of Histochemistry and Histopathology, RPMs, Hammersmith Hospital, Du Cane Rd, London, Unit of Veterinary Cellular and Molecular Biology, Royal Veterinary College, London and Laboratory of Molecular Biology, NIMR, London) A construct comprising the putative regulatory sequences of arg-vasopressin and the Simian virus 40 (SV40) regions coding for large T-antigen was prepared and inserted into the mouse genome in order to study in vivo the effects of the expression of the SV40 oncogene. The offspring of these mice developed neoplasms of the pituitary and pancreatic β-cells. Immunocytochemistry was used to characterise these tumours. The pituitary growths failed to show immunoreactivity to antisera against pituitary hormones, vasopressin or a wide range of other hormonal peptides and general neuroendocrine markers. The endocrine tumours of the pancreas showed immunoreactivity for insulin with occasional scattered cells containing other pancreatic hormones, particularly pancreatic polypeptide. At the ultrastructural level, the endocrine nature of the pituitary lesions was defined by their content of granules, albeit sparsely distributed, and the pancreatic tumours had well-developed β granules. In both lesions, SV40 large T-antigen could be immunostained in the nuclei and shown, by electron microscopy, to occur in the heterochromatin. If these tumours are a result of the inheritance and expression of SV40, this may prove to be a useful model for the human multiple endocrine neoplasia Type I syndrome.

Detection of the acetaldehyde adduct on hepatocyte membranes of rats fed ethanol

A J K WILLIAMS, R E BARRY, K YOUNG, AND M HOPTON (Department of Medicine, Bristol Royal Infirmary, Bristol) We have previously shown that acetaldehyde can bind (adduct) to amino acid residues in hepatocyte membrane proteins and this can activate complement and stimulate neutrophil degranulation and superoxide release.

We have therefore determined the presence of acetaldehyde adducts in vivo on the hepatocyte membranes of rats fed 10% (v/v) ethanol for 12 months±dilufluram (100 mg/kg (o) daily). Liver membranes were prepared by rapid percoll centrifugation, and the amino acid profiles after acid hydrolysis were determined by a photometric ninhydrin method. The position of the acetaldehyde-lysine adduct was determined by incubating poly-lysine with acetaldehyde, and this adduct was detected on the membranes of 23% (three of 13 rats) fed ethanol, and in 40% (two of five) fed ethanol and dilufluram, but not in control rats (not fed ethanol). The mean adduct peak sizes for both groups were similar. No acetaldehyde adducts with other amino acids were detected.

Therefore lysine residues within liver membrane proteins are the major site of acetaldehyde adduct formation in vivo. The variable expression of the adduct may determine why only a proportion of alcoholics develop cirrhosis.
Activated complement is cytotoxic to isolated rat hepatocytes

A J K Williams, S K Moule, J D Mcgivan, and R E Barry (Department of Medicine, Bristol Royal Infirmary, Bristol) Activated complement forms a terminal membrane complex which can lyse susceptible cells. Complement activation has been shown to occur in vivo in PBC, and we have shown that acetaldehyde modified hepatocyte membranes will activate complement and this may be hepatotoxic in alcoholic liver disease. We have therefore studied the effect of activated complement (AC) upon hepatocyte viability as assessed by cellular ATP levels and gluconeogenesis. Isolated rat hepatocytes prepared by the method of Krebs (1974) were incubated in Krebs-Henseleit bicarbonate buffered medium, pH 7.4, 37°C for 60 mins with complement activated via the classical pathway (by pre-incubating with anti-albumin antibody, 37°C, 30 min). ATP levels were significantly reduced in the hepatocytes exposed to AC compared with controls (not exposed to sera) after 20 mins incubation (from 11.8±0.79 nmol ATP/mg hepatocyte protein, mean±SEM, n=5 to 7.5±0.9, n=5, p<0.01) and after 40 mins (6.8±0.77, n=5). Sera without prior activation of complement caused no significant reduction in ATP (11.5±1.0, n=5 at 20 mins, 11.8±0.79 at 40 mins). Gluconeogenesis was reduced in the hepatocytes exposed to AC (2.08±0.5 nmol glucose/mg protein/min, n=4) compared with controls (4.7±0.33, n=4, p<0.01). Activated complement is cytotoxic to isolated hepatocytes and could therefore be an important cause of hepatotoxicity in vivo.

Is sympathetic activity really increased in cirrhosis with ascites?

A J Macgilchrist, L G Howes, C Hawkins, J J Reid, and T J Thomson (University Department of Materia Medica, Stobhill Hospital, Glasgow) The increased plasma norepinephrine (NA) recently reported in severe cirrhosis may be due to increased spillover into plasma from sympathetic nerves (and by implication, increased sympathetic activity), or to reduced clearance of NA due to reduced hepatic metabolism. We have developed a new method to calculate NA spillover and clearance by intravenous infusions of sub-pressor doses of tritiated NA. We studied 14 cirrhotics with ascites and 13 age-matched patient controls. All subjects studied were in-patients, off diuretic therapy and receiving 40 mmol of sodium/day. The cirrhosis was alcohol induced in all but two cases, but no subject consumed alcohol within one week of this study. Values were median (range) and comparison was by Mann Whitney U test.

Thus the clearance in plasma NA in cirrhosis+ascites represents a marked increase in global sympathetic activity rather than any reduction in clearance. This could partly explain both sodium retention and renal vasocostriction, and favours the 'underfilling' theory of ascites formation.

Oxygen free radicals do not activate thezymogens of human pancreatic proteases

P M Guyan, J Butler, and J M Braganza (The Medical School, University of Manchester, Oxford Road, Manchester) The current interest in superoxide (O2-) and hydroxyl (OH) free radicals as the initiating mechanism in pancreatitis, led us to investigate their effect on pancreatic proteases, zymogens and trypsin inhibitor. Equal concentrations of these free radical species were generated, in different doses, using a caesium source (0.5–13 krads) and a linear accelerator (3–15 krads). Using specific substrates and sensitive fluorometric assays it was confirmed that trypsinogen, chymotrypsinogen and proclastase in human pancreatic juice were not activated upon irradiation, whilst trypsin inhibitor was also unaffected. A dose dependent (0.5–2 krads) loss of trypsin activity was observed in dilute aqueous solutions of the pure enzyme, but not in activated human pancreatic juice (doses 0.5–15 krads), whereas in the juice there was a dose dependent loss of chymotrypsin activity.

These in vitro studies indicate that if O2- and/or OH are involved at the initiation stage of pancreatitis, they exert their damage by mechanisms that do not involve activation of pancreatic protease precursors. This resistance to oxidative stress could be due to the presence, in pancreatic juice, of a recently described novel enzyme that scavenges hydrogen peroxide.

Carbohydrate sequencing of a new pancreatic cancer glycoprotein marker

C K Ching and Jonathan M Rhodes (University Dept of Medicine and Walton Hospital, Liverpool) We have recently identified a 3.5×10^6 D serum glycoprotein that is highly specific for pancreatic cancer and distinct from previously described cancer markers (Gut 1987; 28: A372). We have now sequenced its carbohydrate side chains by sequential degradation and lectin binding.

The undegraded pancreatic cancer glycoprotein binds the lectins peanut agglutinin (PNA, gal 1–3 galNAc binding), ulixec (EUA I, fucose, limax flavus (LFA, sialic acid) and wheat germ agglutinin (WGA, sialic acid, NAc glucosamine). Serum containing the marker was electrophoresed (SDS-PAGE, 2–16%) and blotted onto nitrocellulose paper. The blot was subjected to mild acid hydrolysis (50 mM H2SO4) followed by Smith degradation (sequential sodium periodate (75 mM), sodium borohydride (0.1 M) and sulphuric acid (25 mM)). Peroxidase tagged lectins were used to analyse terminal carbohydrates at each step. Mild acid hydrolysis consistently eliminates LFA and EUA I binding. Smith degradation then causes loss of PNA binding with retention of WGA +.

The pancreatic cancer marker epitope therefore comprises: galactose β 1–3 NAc galactosamine-R. fucose sialic acid

Persistence of WGA + on epitope negative side chains after Smith degradation implies that expression of the marker results from incomplete glycosylation.

Difluoromethyl-ornithine (DFMO) inhibits adaptive ileal mucosal hyperplasia after pancreaticobiliary diversion (PBD) in the rat

T Bamba, S Vaja, G M Murphy, and R H Dowling (Gastroenterology Unit, Guy’s Campus, UMDS of Guy’s and St Thomas’ Hospitals, London) Pancreaticobiliary diversion, achieved by transposing 50 cm of jejunum to lie between pylorus and ampulla, stimulates ileal mucosal hyperplasia but the role of polyamines and related enzymes (ornithine decarboxylase: ODC and diamino oxidase: DAO) in this adaptive response, is uncertain. Since ODC is inhibited by DFMO, we studied the effects of 2% DFMO in drinking water on indices of mucosal mass, ODC, DAO, and alk phosphatase activities and polyamine levels in six groups of rats studied two weeks after surgery: (i) transections-controls (TRC), (ii) TRC+DFMO (starting three days pre-op), (iii) TRC pair-fed with group (ii), (iv) PBD, (v) PBD+DFMO and (vi) PBD pair-fed.

Ornithine decarboxylase activity (nmol h−1/10 cm5) increased from 2.6±0.5 SE M0.47 in TRC TO 6.87±2.38 (PBD; p<0.05) but...
DFMO markedly inhibited ODC to 0.45±0.05 (TRC; p<0.001) and 0.75±0.21 (PBD; p<0.002); pair-feeding had no sig effect. There were corresponding changes in putrescine and spermidine but not in spermine. Alk phos activity increased 4–6 fold after PBD but was unaffected by DFMO or pair-feeding. Conversely, DAO activity fell after PBD in both ad-lib and pair-fed groups but did not change with DFMO. Difluoromethyl ornithine inhibited PBD-induced increases in mucosal wet wt, prot and DNA/10 cm by 34%, 31%, and 47% respectively (p<0.05–0.01).

The results confirm that ODC and polyamines play a vital role in the cellular control of intestinal adaptive growth.

Is continuous ambulatory monitoring of duodenogastric reflux feasible? In vitro assessment of an enzymatic amperometric bile acid electrode

D ARMSTRONG, B LENNOX, J ALBERY, G M MURPHY, AND R H DOWLING (Gastroenterology Unit, Guy's Campus, UMDS and Dept Physical Chemistry, Imperial College, London) Duodenogastric reflux (DGR) has been implicated in the pathogenesis of gastric mucosal damage. Current DGR quantitation techniques provide only intermittent or short term monitoring of an episodic phenomenon. Our aim is continuous 24 h ambulatory monitoring of DGR, using intragastric total BA concentrations ([BA]) as a marker of DGR – analogous to pH monitoring in the investigation of reflux oesophagitis. Any [BA] monitoring technique must be sensitive, specific, stable and able to detect all intragastric BA. We therefore used the established enzyme reaction as the basis for a BA electrode. A platinum disc, coated with a conducting organic salt (NMP-TCNQ), is covered by a membrane enclosing the 3-α OH steroid dehydrogenase. 3-α BAs are oxidised by the enzyme, producing NADH which is then oxidised by the NMP-TCNQ, returning NAD⁺ as substrate for the enzyme. Oxidation of NADH generates a current proportional to [NADH], and thus to total [BA] in solution. The semi-permeable dialysis membrane controls BA entry and prevents enzyme loss. We describe the in vitro assessment of this electrode using solutions of chenodeoxycholic acid, deoxycholic acid and their glycine and taurine conjugates (0.1–2.0 mM). Maximum plateau current was generated with each [BA] within three minutes and remained stable for at least 10 minutes. The electrode showed a curvilinear current v [BA] relationship (at 1 mM, 0.61±SE 0.04 μA/mM, n=6). Over 30 hours there was a fall off in electrode response (at 1 mM, 0.34±0.03 μA/mM) attributable to decreased enzyme activity. The electrode was then compared with the standard spectrophotometric assay in determining the total [BA] in methanolic extracts of 10 gastric aspirates, good agreement being obtained (r=0.99, p<0.001). With further development, including miniaturisation and computerised correction for enzyme decay, this electrode should prove suitable for in vivo monitoring of intragastric BA activity and DGR.

An integrated study of gall bladder (BG) motor function in gall stone patients

P PORTINCASA, P MITRA, M MAGHSOUDLOO, G M MURPHY, AND R H DOWLING (Depts of Medicine and Pathology, Guy’s Campus, UMDS and St Thomas’ Hospitals, London) Gall bladder emptying in response to exogenous or meal stimulated CCK is impaired in gall stone patients but few studies have related cholecystokineti cs to quantitative histology of muscle mass or the degree of inflammation in the GB wall. Therefore in longitudinal strips of fresh GB’s, we studied tensiometric contractile responses to CCK-OP (0.875×10⁶ to 1.0 M) and acetyl choline (ACH: 5×10⁻³ to 1.0⁻⁴ M), recording the max tension produced, and relating the dose required to generate 50% max response (D₅₀) to muscle area (MA% of total cross sectional area) and an inflammatoty score (6 parameters).

In 14 patients with moderate chronic cholecystitis there was myohypertrophy, the MA% of 15.0±SEM 1.43 being greater (p<0.001) than that in four histologically normal GB’s (7.72±0.24). The MA% correlated (r=0.62; p<0.005) with the CCK D₅₀ which was also greater in inflamed (3.45±0.006) than in normal (0.54±0.10 mM) GB’s but less ACH was required for the D₂₅ (6.38±1.3 v 15.0±9.9 μM) – perhaps because of denervation hyper-sensitivity. The max tension (kg/cm² muscle) in response to CCK was comparable in normal (0.29±0.05) and inflamed (0.31±0.05) GB’s but after ACH, it was greater in normal (0.35±0.15) than in cholecystitis (0.19±0.02).

These results confirm our in vivo findings and suggest that despite myohypertrophy, the inflamed GB is less responsive to CCK, but more sensitive to ACH, than normal.

Restitution of colon mucosa in vitro

P H ROWE, N L K FAGG, AND R C MASON (Departments of Surgery and Pathology, UMDS, Guy’s Hospital, London) It has previously been reported that complete restitution of epithelial integrity in amphibian gastric mucosa occurs in vivo within four to six hours after injury by IM NaCl. The process of restitution has not been previously described or investigated in the colon. Using chambered bullfrog colon mucosae (n=10) exposed to IM NaCl in the luminal chamber exhibited an immediate fall in potential difference (PD) from baseline values of -58±6.6-3 mV (±SEM) to 0 mV (p<0.05) and a fall in resistance (R) from 216±18.3 Ω cm² to 8±4.8 Ω cm² (p<0.05). Tissues removed (n=5) following NaCl exposure exhibited severe surface mucosal injury with denudation of the basal lamina. After 10 minute NaCl exposure, and replacement of NaCl with Ringer’s solution, at luminal pH 5.0 when tissues (n=5) were allowed to recover for four hours in the chambers, there was histological reconstitution of the surface epithelium and the PD and R had returned to -43±4.5 mV and 220±14.2 Ω cm² respectively, not significantly different from the PD and R observed in control tissues maintained for four hours in the chambers. Control tissues (n=4) showed no significant change in PD or R and no histological evidence of damage.

We conclude restitution of the amphibian colon mucosa occurs in vitro following injury by IM NaCl.

Effects of starvation and refeeding on electrogenic ion transport in the rat colon: a model for famine diarrhoea

HELEN NZEGWU, A YOUNG, AND R J LEVIN (Department of Physiology, University of Sheffield, Western Bank, Sheffield) The aetiology of the diarrhoea induced by famine and by subsequent refeeding of victims is unknown. In the rat model, starvation hypersensitises the small intestine to secretagogues resulting in greater fluid and electrolyte secretion, but little is known concerning the colon. Male rats were progressively starved for up to 72 h and then refeed for up to a further 72 h. Electrogenic ion transport was measured as the short circuit current (Isc) under basal conditions and with bethanecol (1 mM) stimulation. Basal Isc fell during starvation, a maximum decrease of 18% (p<0.05) occurring after 72 h (n=29) compared to fed controls.
(n=26). It then increased over the 72 h refeeding period until it exceeded the fed levels by 18% (p<0.05, n=12). Benthacol stimulated Δ Isc (Δ Isc=Max Isc – Basal Isc) increased significantly after 48 h of starvation (+40%, p<0.01, n=10) and remained at this raised level. On refeeding it returned to the fed level only after 72 h (+12%, n=12, p<0.05). These results may partially explain the famine diarrhoea and the diarrhoea associated with realimentation in man. Support from the British Digestive Foundation is acknowledged.

Atrial natriuretic peptide influences electrolyte transport in the large intestine

K M JOMIAIY, N B HIGGS, M LEES, A TONGE, G WARKHURST, AND J A TURNBERG (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) Atrial natriuretic peptide (ANP) possesses potent diuretic and natriuretic properties and appears to play a central role in fluid and electrolyte homeostasis by an action on the kidney. We examined the influence of ANP on the large intestine, because this organ is also intimately involved in homeostasis. Segments of distal colon of male Sprague-Dawley rats were stripped of muscle layers and mounted in flux chambers. Atrial natriuretic peptide, when added to the serosal aspect of the mucosa, in concentrations ranging from 10-2 to 10-5 M, caused a rapid, dose-dependent rise in short-circuit current (Isc) and transmucosal electrical potential difference (PD). Atrial natriuretic peptide (10-5 M) elicited a peak increase in Isc of 59±2±6-7 μA/cm2 (n=8, p<0.001) and in PD of 2-97±0-3 mV (n=8, p<0.001). A rise in Isc and PD is generally associated with enhanced secretion. The response to ANP (10-5 M) was, however, virtually abolished by pre-treatment with the calcium channel blocking drug, d1-verapamil (10-5 M mucosally and serosally), and also by using a calcium-free (no calcium+2×10-4 M EGTA) solution on the serosal surface.

These findings support a role for ANP in the regulation of colonic ion transport and suggest that ANP may elicit secretion via a calcium mediated mechanism.

SMALL INTESTINE

Somatostatin analogue SMS 201-959 in the dumping syndrome: effect on packed cell volume (PCV)? Blood glucose (BG) and plasma GI peptides

J N PRIMROSE, D JOHNSTON, C SHAW, AND K D BUCHANAN (University Department of Surgery, Leeds General Infirmary and Department Metabolic Medicine, Queens University, Belfast) The aim of this study was to determine the effect of SMS on the dumping syndrome (DS) provoked by hyperglycemic glucose, and on the accompanying changes in PCV, BG, and GI peptides (insulin, N-terminal-glycogen-like immunoreactivity (N-GLI), GIP, VIP, neurotensin and N terminal neurotensin immunoreactivity (N-neuro)).

Dumpling was provoked in 10 patients with DS by means of 350 ml 25% glucose. Patients received placebo, SMS 50 μg or SMS 100 μg, given in random order on separate days. Blood samples were taken for PCV, BG, and GI peptide estimations throughout the two hours of the test.

With placebo, all patients experienced severe symptoms: nine had early dumping and three, late dumping. Symptoms were abolished or much reduced after either dose of SMS.

Somatostatin analogue is effective in treating the symptoms and reversing the changes in PCV and BG of dumping provoked by hyperglycemic glucose. The increments in GI peptides are reduced significantly by SMS, but only the change in N-GLI correlates with the change in PCV (RS=0.82, p<0.05). N-GLI may reflect, or be associated with, the changes of dumping.

Prostaglandin (PG) F2 is a mediator of 5-hydroxytryptamine (5-HT) induced fluid secretion in the human jejunum

I K MUNCK, A MERTZ-NIELSEN, K WESTH, K BUKHAYE, E BEUBER, AND J RASK-MADSSEN (Depts of Medical Gastroenterology, Bispebjerg, and Herlev Hospitals, Univ of Copenhagen, Denmark and Exp Clin Pharmacol Univ of Graz, Austria) Studies in the rat jejunum in vivo have shown that 5-HT causes fluid secretion accompanied by luminal PGE2 release. These effects can be blocked by indomethacin and ketanserin, suggesting that PGE2 may be an important intermediate in the transduction mechanism leading to 5-HT induced secretion. To test this hypothesis in man ‘steady state’ perfusions (9 ml/min) of 30 cm proximal jejunum were performed in eight healthy volunteers, using a triple-lumen tube and a Ringer’s solution with 4Cr-EDTA as a non-absorbable marker. The effects of exogenous 5-HT (10 μg/kg/min iv) on fluid transport and jejunal flow rate (JFR) of PGE2, before and after the administration of indomethacin (1-0 mg/kg iv), were measured in 15-min periods for 2×60 min following a 60 min control period. 5-HT reversed fluid secretion (+1.9±0.7 ml/h/cm; mean±SE) into profuse secretion (-1.7±0.5; p<0.01). Duncan’s multiple range test and significantly increased JFR of PGE2 (0.11±0.03 vs 0.40±0.10 ng/min; p<0.01). Indomethacin partly restored fluid absorption (+1.2±0.5; p<0.01) and slightly inhibited JFR of PGE2 (0.21±0.4; p<0.05). These results provide further evidence in support of the theory that PGs are involved in intestinal fluid secretion induced by 5-HT.

Human upper gastrointestinal transit and carbohydrate absorption are modulated by beta-adrenoceptors

A S MCEINTYRE, D G THOMPSON, W R BURNHAM, AND E WALKER (Dept Gastroenterology, The London Hospital (Whitechapel), London and Oldchurch Hospital, Romford, Essex) Control studies: Orocecal transit of a soup lactulose meal was measured in 26 subjects by the serial breath hydrogen method. Carbohydrate absorption was estimated with a series of fructose meals, fructose being varied in 10 g increments (20-90 g); the smallest dose producing a hydrogen rise indicated that the absorptive threshold was just exceeded. Transit was consistent within, but varied widely between individuals (median 55, range 32-172 min).

Fructose absorptive threshold showed a similar interindividual variation (median 40, range 30-80 g), and correlated with transit (T=0-70, p<0.001).

B-adrenergic stimulation: Isoprenaline (B1 and B2) consistently inhibited transit (mean Δ 40±4±3±7 mins, p<0.001) and increased fructose absorption (mean Δ 15 g), the magnitude of response varying inversely with control data (T=−0.52, p<0.01). Atenolol (B1 antagonist) abolished the effect.

B-adrenergic blockade: B-blockade (B1 and B2 or B1 alone) accelerated transit (mean Δ 21±7±2±4 mins, p<0.02) and reduced fructose absorption (mean Δ 15 g); the effect was directly related to control transit (T=−0.49, p<0.02).

Thus a tonically active B1-adrenoceptor pathway modulates normal nutrient transit and carbohydrate absorption and accounts for up to 67% of differences between individuals.

Charactrisation of defective sodium coupled glucose transport in congenital
Phosphatidylcholine (PC) degradation in small intestinal bacterial overgrowth

M HEALY, M G O’CONNOR, C T KEANE, D G WEIR, AND R R O’MOORE (Depts of Clinical Medicine, Clinical Microbiology and Biochemistry, St James’ Hospital and Trinity College Dublin, Ireland) In vitro experiments with anaerobic bacterial strains, frequently found in small intestinal bacterial overgrowth (SIBO), show enzymatic activity capable of degrading the choline moiety of PC to the aliphatic amines (AA), trimethylamine (TMA) and dimethylamine (DMA). Since PC plays an important role in lipid absorption, a study was undertaken to assess the PC degradation pathway, using a rat self-filling blind loop model (SFBL, n=10 and controls, n=6) and SIBO patients.

Animal study: Urinary excretion of AA’s was measured on a choline free diet (PC 2 g/kg dry food). SFBL DMA excretion was greater than controls (14±2 v 5±0.9 mmol/day, X±SE, p<0.005). Antibiotic treatment reduced SFBL DMA from 13±1 to 2±3 ±0.6 mmol/day, p<0.02. To confirm the pathway from PC to AA. orogastric intubation was performed with (N-methyl-H) PC and ‘H-DMA identified in the urine.

Human study: 10 controls and 12 SIBO patients (jejunal culture 10³ orgs/ml) were given a fatty meal to stimulate biliary PC. Urine 4-hr AA excretion was measured and results expressed as total AA (DMA+TMA)/creatinine ratios. The excretion ratio was greater in SIBO patients, 98±22 v 33±3 (controls), p<0.02. This study indicates greater PC degradation in both the animal model and SIBO patients. Antibiotic treatment reversed this effect in the animal model. The bacterial degradation of PC may be a factor in the pathogenesis of the steatorrhoea in SIBO.

Influence of orally administered amino acids and peptides on protein turnover kinetics in the short bowel syndrome

R G REES, G K GRIMBLE, D HALLIDAY, C FORD, AND D B A SILK (Department of Gastroenterology – Central Middlesex Hospital London, Acton Lane, London and Clinical Research Centre, Harrow) Experimental evidence supports the use of peptides rather than amino acids (AA) as the N source in elemental diets. In this prospective randomised cross-over study, two isonitrogenous, isoaloric diets with identical AA composition were administered to four malnourished patients with the nutritionally inadequate short bowel syndrome (<100 cm). Each received a five day ‘run in’ period of enteral nutrition and were then randomised to receive a diet containing either a partial hydrolysate of casein (PEP) or the equivalent mixture of free AA. After a further five days the alternative diet was given and on completion of each study period, whole protein turnover was measured by a primed, constant infusion of 13 C-lysine. There was no significant difference in the rates of flux, synthesis, breakdown or oxidation during administration of the PEP as compared with the AA diet. Cu (II) Sephadex chromatography showed that 50% of alpha amino N in the PEP diet was present as tetra- or higher peptides. These findings indicate therefore that in the short bowel syndrome there are no apparent short-term nutritional advantages of administering a diet whose nitrogen source is composed of medium chain length peptides.

Application of organ culture to the investigation of lectin-induced damage to the brush border membrane

R M BATT, C A HART, I. MCCLEAN, B GETTY, AND J R SAUNDERS (Departments of Veterinary Pathology, Medical Microbiology and Microbiology, University of Liverpool) Ingestion of lectins such as phytohaemagglutinin in red kidney beans is an important cause of food poisoning, but the pathophysiological mechanisms are poorly understood. Lectins bind to specific carbohydrates in brush border glycoproteins, but the relationship between binding and lectin-toxicity is unclear. In this study, the ultrastructural effects of lectins on the brush border were examined during organ culture and related to their receptor specificities. Explants from rabbit ileum were cultured for 24 hours in medium containing each of 10 lectins, and were then processed for electron microscopy. Phytohaemagglutinin and lectins with specificity for N-acetyl glucosamine or N-acetyl neuraminic acid caused distinct damage to the brush border membrane at concentrations between 10 and 100 μg/ml. The most constant feature was elongation and vesiculation of microvilli which in some cases appeared to be joined at the tips. In contrast, lectins with specificities for glucose, mannose, galactose or N-acetyl galactosamine had no discernable effects even at 200 μg/ml, a concentration considerably higher than that required for haemagglutination. These findings provide evidence for ultrastructural damage to the brush border membranes by specific lectins. The apparent relationship between damage and receptor specificity may reflect either accessibility of appropriate binding sites or a differential response to binding.

Postoperative pain relief with diclofenac suppositories

R F H DAWES AND G T ROYLE (University Department of Surgery, Southampton General Hospital, Southampton) Diclofenac is a non-steroidal analgesic and has a long half life (12 hours) when given as a suppository. The purpose of this study was to investigate its role as a post-operative analgesic for abdominal surgery. Sixty nine patients having elective abdominal surgery were entered into a prospective randomised double blind trial of diclofenac (Voltarol, Geigy) as an adjunct to standard im opiate postoperative analgesia. Patients received...
eight suppositories over four days – that is, 12 hourly, containing either 100 mg diclofenac or inert substance. Abdominal pain was recorded by the patients regularly on a 10 cm visual analogue scale (VAS) after operation, both ‘at rest’ and after coughing. Patients were closely monitored for any unwanted symptoms or complications, and all drugs administered were recorded. Thirty one diclofenac and 26 placebo patients fully completed the study. Daily pain scores measured ‘at rest’ were similar between groups. On coughing diclofenac patients experienced consistently and significantly (p<0.02) less pain on all the post op days. Opiate analgesic consumption was similarly reduced in the diclofenac group. There were no differences in post-operative complications between the group. It is concluded that diclofenac is of use in post abdominal surgery pain relief when given 12 hourly as a 100 mg suppository.

**Small Intestine**

**Use of endoscopic biopsies to diagnose disaccharidase deficiencies**

J A SMITH, J AMOAH, D O'REILLY, J F MAYBERRY, AND R G LONG (Medical Research Centre, City Hospital, Nottingham) Endoscopic duodenal biopsies can replace Crosby capsule jejunal biopsies for the histological diagnosis of malabsorption despite the presence of shorter villi and Brunner’s glands. As endoscopic biopsy is quicker and easier to perform, we compared disaccharidase levels in endoscopic biopsies from the second part of the duodenum and Crosby capsule biopsies from the proximal jejunum. Thirty patients had normal histology and 12 patients had partial or total villous atrophy. Two normal patients had primary hypolactasia diagnosed by both biopsy techniques. Mean±SEM lactase levels in 28 normal duodenal biopsies were 12.1±2.3 U/g protein, and in jejunal biopsies were 21.2±4.0 U/g protein (p<0.01). A parallel statistically significant reduction in the duodenum was seen for maltase and sucrase results. In villous atrophy secondary disaccharidase deficiencies were found and corresponding lactase results were 2.0±0.6 and 4.0±1.2 U/g protein. Thus normal jejunal levels are consistently higher than duodenal levels but results in villous atrophy are not statistically different. We conclude that duodenal biopsies are a valid alternative to Crosby capsule jejunal biopsies for the diagnosis of both primary and secondary disaccharidase deficiencies.

**Concomitant presence of IgE plasma cells in duodenal and bronchial mucosa in asthmatic patients**

ANDRÉ C, GINDRE D, PACHECO Y, DESCOS I, AND M PERRIN-FAYOLLE (Laboratoire d’Immunopathologie Digestive INSERM, Centre Hospitalier Lyon-Sud, Pierre-Benite, France) Immunoglobulin-containing cells of all classes were counted according to the tissue unit method in duodenal and bronchial mucosa in control subjects and asthmatic patients.

In control subjects (n=6) the mean percents of IgA, IgM, IgG, IgD, and IgE cells were 74, 8, 17, 1, and 0 respectively in the bronchial mucosa. In 25 control subjects the mean percentages of IgA, IgM, IgG, IgD, and IgE cells were 75, 13, 10, 1, and 1 respectively in the duodenal mucosa. The same studies were performed in 15 asthmatic patients. The differential counts of IgA, IgM, IgG, and IgD cells did not differ from the values observed in controls.

A significant increase of IgE cells was found in the duodenal and bronchial mucosa from nine patients, the average values being 13% in the digestive mucosa and 24% in the respiratory mucosa. No IgG plasma cells were observed in the mucosa from five other patients. In the last patient there were no IgE cells in the intestinal mucosa but these cells accounted for 18% in the respiratory mucosa.

The similarities of the local allergic response in asthmatic patients may be interpreted in three ways. Food allergy may be involved in many asthmatic patients. The immune response could be the consequence of an allergic stimulation at both levels. The observed data also correspond to the concept of an universal mucosal immune system: cells stimulated at one mucosal site may migrate to other mucosal sites.

**Feedback regulation of transit and motility in the human jejunum and ileum by ileal infusion of glycochenodeoxycholic acid (GCDC)**

PENAGINI R, C SPILLER R, J J MISIEWICZ, AND P G FROST (Depts of Gastroenterology and Nutrition, and of Chemical Pathology, Central Middlesex Hospital, London) The present study examined the possibility that presence of GCDC in the human ileum in amounts comparable to a bile acid pool (5 mmol) inhibits fed ileal and jejunal motility. Ten healthy subjects were studied. Transit times (by a marker bolus of bromosulphthalein), intraluminal pressure activity, flow rates (by 14C-PEG) and intraluminal bile acid concentrations (BA) were measured in a 40 cm jejunal segment proximal (n=6) and a 40 cm ileal segment distal (n=6) to an ileal port inducing an isotonic electrolyte solution with or without GCDC for 80 min. During GCDC infusion (60 mmol/min) jejunal and ileal transit were markedly (p<0.05) delayed (31±6.7 to 21±5.8 min, v 21±3.5 min, respectively), while flow rates did not change significantly (4.5±0.6 to 4.5±0.6 ml/min and 4.8±0.5 v 4.2±0.3 ml/min, respectively). Per cent duration of pressure activity in the ileum decreased (p<0.05) promptly (60±8 sec) after the start of GCDC infusion (6.9±1.6 v 7.9±4.2 sec). Inhibition of jejunal motility was more gradual and reached significance (p<0.05) only 30 min after start of GCDC infusion (18.9±5.2 v 35.2±7.1). Ileal BA were not altered by GCDC infusion, while intraluminal BA increased (p<0.05) during GCDC infusion and showed a 35–92% (median 45%) absorption of GCDC by the 40 cm ileal segment.

In conclusion these observations suggest the existence of a regulatory mechanism in the healthy man, whereby presence of GCDC in the ileum inhibits motility and delays transit throughout the small intestine.

**Wheat protein, gut abnormalities and rheumatoid arthritis**

CIRNA O’FARRELL, D MARTEN, D MELCHER, R W SHERWOOD, A J GOLDSTEIN, L FERNANDES, AND B MACDOUGALL (School of Biological Sciences, University of Sussex and Depts of Histopathology, Biochemistry, Rheumatology, and Gastroenterology, Royal Sussex County Hospital, Brighton, Sussex) There is increasing interest in the role of the GI tract in the pathogenesis of rheumatoid arthritis (RA). We studied this role in 87 RA patients (65 women; mean age 62). Using ELISA, 50 of the 87 had raised levels of IgG to wheat and/or milk protein (41 were positive for wheat, six for milk and 12 for both). Ninety per cent of the antibody positive group had raised levels of IgA and rheumatoid factor (RF) compared with only 27% (p<0.001) of antibody negative patients (both groups were on similar treatment regimens).

Jejunal biopsies were carried out on 25 of these patients: 15 had raised levels of both IgA RF and wheat protein IgG (AB+); the remaining 10 had normal levels of both antibodies (AB–). The biopsies were...
assessed using standard histological, stereo-
logical and biochemical techniques. Villous
atrophy was present in six of the AB+ but in
only one of the AB- patients. This was
confirmed by a lower villous surface/volume
ratio (77.8±17.3 SD) in AB+ patients when
compared with AB- (97.9±21.8; p<0.02)
or 10 age-matched control patients (125±
17.9; p<0.001). Lactase levels (measured as
umol/min/g tissue) were also lower in the
AB+ group (3.4±2.0 SD) than in the AB-
(5.7±2.5; p<0.03) or control groups
(6.4±2.7; p<0.001).

These findings of GI abnormalities
associated with raised levels of IgA RF and
wheat protein IgG in our patients suggest
that the gut may be involved in the immuno-
pathogenesis of RA.

Familial visceral myopathy

C A RODRIGUES, N A SHEPHERD, P R HAWLEY, J
E LENNARD-JONES, AND H H THOMPSON (St
Mark's Hospital, City Road, London, The
London Hospital (Whitechapel), London)
The first British kindred with autosomal
dominant visceral myopathy is described:
Six affected members in two generations all
had intestinal pseudo-obstruction which
was demonstrated by contrast radiology.
Five of these patients had a megadu-
denum, two had diminished oesophageal
peristalsis, four small bowel and four
colic involvement. One patient had
dilatation of one ureter and incomplete
bladder emptying on intravenous
urography.

The clinical onset of the disease occurred
in childhood or adolescence with dysphagia
(n=2), abdominal pain (n=5), abdominal
distension (n=6), constipation (n=4),
diarrhoea (n=4), and urinary symptoms
(n=2). The two most severely affected
individuals are on home parenteral
nutrition and have undergone surgery for the
alleviation of symptoms. Three other
patients have mild, non-progressive
symptoms, and have been able to maintain
normal nutritional status without special
measures. The sixth family member has
been lost to follow up, and his current status
is unknown.

The main pathological features consisted of
marked dilatation and thinning of the
bowel wall, and vacuolar degeneration of the
longitudinal layer of the muscularis
propria with fibrosis and elastosis. The
submucosal and myenteric nerve plexuses
appeared normal and there was no histo-
logical abnormality of the blood vessels.

Is long term home parenteral nutrition
worthwhile?

M A STOKES, J I SHAFFER, M H IRVING (ON
BEHALF OF THE UK HOME PARENTERAL
NUTRITION GROUP) (Departments
of Medicine and Surgery, University of Man-
chester School of Medicine, Hope Hospital,
Salford) There are 241 patients entered on
the HPN register for the United Kingdom
and Ireland. Fifty two of these have been on
HPN for two or more years. There are 33
women and 19 men with an average age of
36 years (range 4–60). Over half have been
entered on the register by the two largest
centres. In fact, five centres account for
over 80% of these long-term HPN patients.

Crohn's disease is the underlying path-
ology in over half, and 68% are on HPN
because of the short-bowel syndrome. They
have been on HPN for a total of 190 years.
Forty one of them are still on HPN, the
longest has been on for seven years. Four
patients have resumed enteral feeding, the
longest 41 months after commencing. Six of
these patients have died, two after five years
on HPN.

These longterm patients have a significa-
cantly better lifestyle (p<0.01), with a lower
incidence of sepsis (0.25 per patient per
year; p<0.05), and a lower incidence of
total complications (0.56 per patient per
year; p<0.001), than for the group of HPN
patients (n=236).

Home parenteral nutrition is a highly
successful treatment in the management of
patients with longterm intestinal failure.

Jejunal mucosal architecture in HIV
infected male homosexuals

P A BATMAN, A MILLER, S FORSTER, A PINCH-
ING, W HARRIS, AND G GRIFFIN (Departments
of Communicable Diseases and Histol-
pathology, St George's Hospital and St
Mary's Hospital Medical School, London)

Crosby capsule jejunal biopsies from HIV
antibody positive male homosexuals (n=20;
asymptomatic five, persistent generalised
lymphadenopathy nine, AIDS=6) were
subjected to light microscopy and stained
with H and E, modified Ziehl-Neelsen,
Giemas, PAS and Gram (to detect mucosal
enteropathogens). Mucosal surface area/
volume ratio (S/V) was determined using
Weibel graticule. Crypt length (CL) was
assessed by counting enterocytes from crypt
base to crypt/villus junction. Intraepithelial
lymphocytes (IEL), detected using immu-
noperoxidase technique (lyucocyte common
antigen), were counted/500

enterocytes for each biopsy. Jejunal biop-
sies from age matched control subjects
(n=seven) were similarly treated. No
mucosal enteropathogens were detected in
any biopsy. Enterocytes appeared normal
and villous atrophy (VA) with crypt hyper-
plasia was the only abnormality detected at
all stages of HIV disease; S/V (control)
49±6.2, (HIV) 38±4.9; p=0.006; CL (control)
32.5±6.8, (HIV) 38±8.7; p=0.049. Crypt length
also inversely correlated with S/V, r=-0.7,
p=0.0005.

Intraepithelial lymphocytes (control)
19±6.5, (HIV) 24±7.9, p=NS

Thus jejunal crypt hyperplastic VA
occurs at any stage of HIV disease. Crypt
length correlates with the degree of VA and
IEL counts are normal.

Glycogenodeoxycholic (GCDC) and
glycolic (GC) acids infused in the human
jejenum inhibit small bowel motility and
transit

R PENAGINI, J J MISIEWICZ, AND P G FRIED
(Departments of Gastroenterology and Nutri-
tion, and of Chemical Pathology, Central
Middlesex Hospital, London) The present
study examined the effect of jejunal infusion
of GCDC and GC on small bowel transit
time (SBTT), lactulose (5 g-hydrogen breath
test), fasting jejunal motility and serum bile
acid concentrations in 18 healthy subjects.

Each subject was studied during jejunal
infusion of saline alone (control) and during
infusion of at least one of four saline solu-
tions containing: (1) GCDC 3.3 mmol
(n=5), (2) GCDC 3.3 mmol+1-leucithin 0.8
mmol (L) (n=5), (3) GCDC 5 mmol+L
(n=6), (4) GC 5 mmol+L (n=6). Each
solution was infused in 80 min on a separate
day in randomised order. Fasting jejunal
motility was recorded in the experiments
testing (3) and (4) only. Blood samples were
collected at 0, 30, 60, 90, 120, 150 min from
start of infusion for measurement of total
bile acids (enzymatic method); integrated
incremental response (BA IIR) was
calculated.

Results (mean±SEM) show that GCDC
5 mmol+L and GC 5 mmol+L delayed
(p<0.05) SBTT when compared with control
infusion (158.3±12.5 min v 111±7±16.7
min and 103.3±21.8 min v 70±0±14±9 min),
hindered (p<0.05) the percentage duration
pressure activity of phase 2 (13.1±1.8% v
28±1±3.4% and 29±2±5.5% v 34±9±3.9%).
but did not change duration of migrating motor complex, or of its phases. Glycochenodeoxycholic 3-3 mmol + L had a less consistent effect on SBTT (p = NS). All four infusions containing bile acids increased (p < 0.05) BA IIRs in comparison with control infusion.

In conclusion these observations suggest a role of endogenous bile acids in the regulation of small bowel motility and transit.

The histopathology and staging of carcinoma of the ampulla of Vater

ICTALBOT, J P NEOPIEGOLOS, D CARR-LockE, AND D SHAW (Dept of Pathology and Surgery, Clinical Sciences Building, Leicester Royal Infirmary, Leicester) Carcinomas of the ampulla are uncommon and data concerning their pathology and behaviour are inconsistent and of questionable reliability. We have analysed the tumour type, grade, pattern of local invasion and outcome in 26 carcinomas surgically resected over a 13 year period. Twenty-five (96%) were intestinal type adenocarcinomas, the degree of differentiation being good (eight), moderate (13), or poor (four). Adenoma coexisted with adenocarcinoma in 11 cases, six of these being well differentiated (low grade). There was epithelial dysplasia of duct epithelium adjacent to 10 carcinomas, only two of these being low grade.

Forty five per cent of patients survived five years. The five year survival rate for the whole series (estimated by the Kaplan-Meier method) was 52% and, with low grade adenocarcinoma, 83% (p < 0.003). Using a staging system, based on extent of local spread (Stage I=invasion of common bile duct wall only, II=infiltration into duodenal wall and/or retroperitoneal adipose tissue, III=infiltration of pancreas, IV=lymph node metastases), long term survival correlates inversely with stage, both along (p=0.0055) and by multivariate analysis, independently of grade. A simple scoring system, combining both grade and stage precisely predicts survival (p < 0.001).

Endoscopic management of inoperable cholangiocarcinoma using Iridium-192

R J EDE, A HATFIELD, S MCTYRE, AND G MAIR (Departments of Gastroenterology and Radiotherapy, The London Hospital, London) Improved survival has recently been reported in patients with inoperable cholangiocarcinoma after intubation by the percutaneous route and intraluminal radiotherapy. We report a less invasive endoscopic technique in which the Iridium-192 wire source is inserted down a nasobiliary catheter placed within a previously inserted endoscopic biliary prosthesis. Six men, mean age 64 years (range 41–80) with inoperable cholangiocarcinoma have so far been treated. Following biliary decompression when the serum bilirubin had fallen substantially radiotherapy was commenced. The Iridium wire was loaded into a 0.038″ Teflon-coated movable core guide wire and inserted through the nasobiliary catheter under fluoroscopic control. A total dose of 6000 rads was administered over a mean of four days (range 3.3–4.8). During this period serum bilirubin increased slightly in three patients but fell again after removal of the Iridium wire. Mean hospital stay after this treatment was 6.3 days (range 1–26). The only complication was mild cholangitis in two patients. Two patients have since required stent replacement. One patient has died 105 days after treatment: the remaining five are all alive between 10 and 430 days. This technique was well tolerated by all patients and in view of the reduced morbidity of endoscopic compared with transhepatic prosthesis insertion should be considered in patients with inoperable cholangiocarcinoma.

Morphological changes in the pancreas, suggestive of endocrine regeneration, induced by transplantation of isolated hepatocytes

V JAFFE, H DARBY, AND H J HODGSON (Depts of Surgery and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) We have shown that transplanted isolated synergic rat hepatocytes grow within the pancreas. Liver cells are found in interlobular spaces and periductular sites up to three months after implantation, and after this a remarkable association is established between liver cells and the endocrine pancreas – hepatocyte-islet rosettes – a halo of liver cells around a core of islet tissue. This report highlights the atypical pancreatic morphology in these animals which appears related to the presence of hepatocytes. The principle changes include an increase in number and size of islets, and regions of diffuse neuroendocrine cells in association with areas of ductular radicles. Histochemical staining has shown these extensive atypical areas to contain functioning endocrine tissue. The appearances are suggestive of pancreatic endocrine neogenesis and regeneration. When combined with a surgical procedure to divert portal blood across the pancreas long term, the pancreatic changes associated with implanted hepatocytes are even more marked.

The disposition of proliferating liver cells as an outer mantle around islets was suggested to be supportive evidence for the existence of pancreatic hepatotrophins. The regenerative pancreatic changes that have been demonstrated raise the possibility of an hepatic pancreaticotrophin.

Faecal chymotrypsin accurately predicts exocrine pancreatic function in infants and children

G A BROWN, D SULE, J W PUNTS, AND I W BOOTH (Institute of Child Health, University of Birmingham, Birmingham) Faecal chymotrypsin measurements have been proposed as an alternative to intraduodenal tests of pancreatic function but with insufficiently rigorous validation. We have reassessed the test by simultaneous measurements of faecal and duodenal chymotrypsin in 30 children aged three weeks to 13 years with exocrine pancreatic function ranging from nil (five), through partial insufficiency (one), to the physiological range (24). Mean faecal chymotrypsin concentration was determined, for each child, from three random stools collected on separate days within 72 hours of a conventional pancreatezymin stimulation test. In the 25 children with measurable duodenal enzyme, the mean faecal chymotrypsin concentration was significantly positively correlated with both apparent chymotrypsin secretion rate and mean duodenal concentration (Spearman’s rank correlation coefficients of 0.63 and 0.45, p<0.001 and <0.01 respectively). The five children with undetectable duodenal chymotrypsin had mean faecal concentrations of only 3–10% of the lower limit of the reference range (120 μg/100 g stool). In the child with partial insufficiency it was 33% of the lower limit. All 24 children with normal function were within the reference range. In 21 neonates with suspected meconium ileus, faecal chymotrypsin was less than 19 μg/g stool in all 16 babies subsequently shown to have cystic fibrosis. Faecal chymotrypsin is a rapid, simple, cheap, readily repeated, non-invasive test which should be done before contemplating intraduodenal testing.
Cytological diagnosis of hepatobiliary and pancreatic malignancy

I S BENJAMIN, T KRAUSZ, P DOMIZIO, S LAZZARA, AND L I H BLOMGART (Hepatobiliary Surgery Unit and Department of Histopathology, Hammersmith Hospital, London) During a six year period 162 patients suspected of malignancy of liver, bile ducts or pancreas were examined cytologically. One hundred and twenty patients had proven malignancy, 41 benign lesions, and one remains uncertain. One hundred and ninety six specimens were examined (118 pre-operative and 78 intra-operative). Malignancy was diagnosed correctly in 81/118 cases (68-6%). Fine needle aspiration (FNA) was more sensitive (80% true positive) than exfoliate cytology (40%). There were no false positive results, but one suspicious result in a patient whose bile duct stricture remains of uncertain nature. Fine needle aspiration of biliary lesions had the highest sensitivity both pre- (77%) and intra-operatively (95%). The overall predictive value of a positive result was 100% (98-8% if the unproven case is included) but the predictive value of a negative result was only 54%. Fine needle aspiration cytology has proved valuable for pre-operative diagnosis, especially in bile duct strictures, and may also aid intra-operative diagnosis in difficult cases. Palliative intubation of suspected biliary tumours without tissue confirmation should now rarely be necessary.

A novel enzyme linked lectin assay compared with RIA CA19-9 as a serum test for pancreatic cancer

C K CHING AND JONATHAN M RHODES (University Dept of Medicine and Walton Hospital, Liverpool) We have recently described a novel serum marker for pancreatic cancer: a 3.5x10^5 D glycoprotein that expresses galactose 1-3 NAc galactosamine (peanut PNA, lectin binding). This marker when present accounts for a high proportion of total serum peanut-lectin binding activity (PLBA). An enzyme-linked lectin assay (ELLA) has therefore been developed to quantify total serum glycoprotein gal 1-3 gal NAc expression. This has been compared with RIA for CA19-9 antigen.

Sera were diluted (1:20000) in carbonate buffer pH 9.6 and coated (16 hrs at 4°C) onto micro-ELISA plates which were then incubated in peroxidase-PNA (12.5 µg/ml) after washing and quenching. Bound lectins were estimated colorimetrically. Activity was expressed in arbitrary units by comparison with a standard curve of a known marker-positive serum. High PLBA (≥10 unit PLBA/ml) was found in 19/32 pancreatic cancer sera, 0/18 normals, 8/20 other cancers, 0/15 pancreatitis, 2/12 benign and 5/8 malignant obstructive jaundice. Eleven of 32 pancreatic cancer sera had normal CA19-9 levels but 4/11 of these contained ≥1 uPLBA/ml. Overall sensitivity for PLBA assay was 90% and specificity 79% (96% if other cancers excluded). CA19-9 in this study had a sensitivity of 66% but combination of the two tests improved this to 78%.

This ELLA is highly specific for malignant disease and seems likely to prove useful as a test for pancreatic cancer, possibly with CA19-9 assay.

GASTRO DUODENAL II POSTERS

Gastric mucosal bleeding: what dose of aspirin is safe?

P J PRICHARD, G K KITCHENMAN, AND C J HAWKEY (Department of Therapeutics, University Hospital, Nottingham) Low doses of aspirin are increasingly recommended for the prevention of vascular disease. They are assumed to be safe but there is no evidence that this is so. We have therefore measured aspirin induced microscopic gastric bleeding to determine the threshold dose for gastric injury in humans. Forty eight healthy volunteers were studied under basic conditions and after taking aspirin 75 mg or 300 mg/day for five and 12 days or aspirin 1800 mg/day for five days. Mucosal injury was quantified as microscopic bleeding intragastri washings aspirated via an orogastric tube two hours after the final dose. Consumption of aspirin for five days increased bleeding from basal values 0.68 µl/10 mins (95% confidence limits 0.42-1.12 µl/10 mins) to 1.32 (1.01-2.31) µl/10 mins (aspirin 75 mg, p<0.01) to 2.38 (1.7-4.2) µl/10 mins (aspirin 300 mg, p<0.01) and to 8.11 (5.36-12.28) µl/10 mins (aspirin 1800 mg, p<0.01). Values at 12 days with aspirin 75 mg (1.27 (0.59-2.72) µl/10 mins), and aspirin 300 mg (2.54 (2.34-9.95) µl/10 mins) were not significantly different from five day values. The bleeding caused by aspirin was dose dependent (p<0.05) and implies a threshold for mucosal injury of about 30 mg/day. Thus even the lowest therapeutic doses of aspirin increased the risk of gastric mucosal bleeding in humans.

Aspirin and bleeding peptic ulcer

P J PRICHARD, K W SOMERVILLE, G FAULKNER, AND M J S LANGMAN (Department of Therapeutics, University Hospital Nottingham, Nottingham) Aspirin intake has been related to upper gastrointestinal bleeding, but the strength of this association has remained unclear. We have reported that other NSAIDs are strongly associated with bleeding peptic ulcer in the elderly. We have analysed the data from this earlier study with respect to aspirin intake.

Two hundred and thirty of 290 patients aged ≥60 admitted with bleeding peptic ulcer between 1983 and 1985 were questioned. Two hundred and thirty hospital controls and 207 of 230 community controls consented to questioning. Patients with bleeding peptic ulcer were more than twice as likely to be taking aspirin than hospital or community controls with relative risks (95% confidence limits) of 2.2 (1.4-3.6) and 3.3 (1.8-6.2) respectively (p<0.001 McNemar's test). These results changed little after exclusion of concurrent takers of other NSAIDs and takers of aspirin for indigestion. Other analgesic intake did not vary significantly between cases and controls. Both bleeding gastric and duodenal ulcer were significantly associated with increased aspirin intake. Respective relative risks being 3.0 (1.3-7.4) and 3.3 (1.4-8.0) (community controls). The attributable risk for aspirin and other NSAIDs in bleeding peptic ulcer was 35% (28-42%) (community controls).

Aspirin intake is significantly associated with bleeding gastric and duodenal ulcer in the elderly. Risks appear to differ little from other NSAIDs.

Effect of simulated upper gastrointestinal (GI) haemorrhage on gastric acid secretion and GI hormones

G M FULLARTON, E J BOYD, G P CREAN, K BUCHANAN, AND K E L MCCOLI (University Dept Medicine, Western Infirmary and Gastrointestinal Centre, Southern General Hospital, Glasgow) It is surprising that the majority of acute upper GI bleeds stop spontaneously despite the adverse acidic environment for clot formation. We have examined the effect of simulated duodenal bleeding on acid secretion and GI hormones in seven healthy volunteers.

Gastric secretion was stimulated with iv pentagastrin infusion (0.25 µg/kg/h). After 4x15 min collections of gastric juice 40 ml blood was vencesected and infused directly into the duodenum before evaculating
every five minutes for 20 minutes. Further 4×15 min gastric collections were obtained after commencement of blood infusions. Corrections were made for pyloric losses and duodenal reflux and any duodenogastric reflux of blood was quantitated. Plasma concentrations of GI hormones were monitored. The effect of duodenal infusion of egg-white which has a similar protein and carbohydrate content to blood was also studied.

After commencement of blood infusions, gastric acid output (mmol/h) fell to 21.4±3.7 (mean±SEM) compared to 29.8±3.3 over the preceding hour (p<0.02). Mean % inhibition was 30.4% (range 17–67). This was due to reduction in volume and (H+) and was not explained by reflux of blood or duodenal juice or incomplete recoveries. Plasma gastric inhibitory peptide (GIP) concentration (pmol/l) increased from 32±2 (mean±SEM) to 66±9 following blood infusion. Egg white did not affect acid secretion or GIP release.

This inhibition of gastric acid secretion by intraluminal blood may be mediated by GIP and represent a physiological response to facilitate haemostasis.

### Intragastriac fibrinolysis in bleeding peptic ulcer disease

K E WHEATLEY, VALERIE A Poxon, P W DYKES, AND M R B KEIGHLEY (Department of Gastroenterology, General Hospital, Birmingham) Bleeding peptic ulcer disease is a common problem with mortality rates of over 10% in many series. Little is known, however, about the aetiology of bleeding or rebleeding in these patients. We have studied the role of the excessive fibrinolytic activity in gastric juice, due to duodenogastric Trypsin reflux. Gastric juice was taken from 32 patients presenting with upper GI haemorrhage (DU-11, GU-9) and 31 control patients (DU-10, GU-8). Fibrinolytic activity of aspirated gastric juice was assessed using fibrin plates, and Trypsin assayed using a colourmetric method. Fibrinolytic activity was found to be present in 20 patients (63%) with upper GI bleeding, and only four (13%) of controls (p<0.005). Trypsin was detected in all gastric juice samples showing fibrinolysis. Fibrinolytic activity was present in 22 out of 29 samples with pH>4, and only two of 34 at lower pH (p<0.005). Fibrinolytic activity was seen in six of 11 patients with bleeding DU (55%), but only one of 10 control DU patients (10%) (p<0.025). There was no significant difference in fibrinolytic activity with bleeding or non-bleeding gastric ulcers.

We conclude that patients with upper GI haemorrhage show increased fibrinolytic activity in gastric juice, compared with non-bleeding controls.

### The effect of submucosal adrenaline on blood loss from standard bleeding ulcers

S C S CHUNG, J W C LEUNG, M GALVINA, AND T W LEE (Departments of Surgery, Medicine and Anaesthesia, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong) To investigate the possible use of endoscopic adrenaline injection to control haemorrhage for bleeding ulcers, we studied the effect of submucosal adrenaline injection on blood loss in a standard bleeding ulcer model in dogs.

Dogs weighing 20–25 kg were anaesthetised using thiopentone and anaesthesia was maintained with halothane and oxygen. Laparotomy was performed and the stomach opened via an anterior gastrostomy. Submucous injections of 3 ml of 1/10000 adrenaline or 10% sodium metabisulphite (carrier substance for adrenaline) was made in the body of the stomach. Standard bleeding ulcers were made in the injected area with the Quinton ulcer-maker. Ulcers made in non-injected areas served as controls. The blood loss in the first three minutes was collected by inverting the ulcer over a small dish and measured by weighing.

Mean blood loss from control ulcers (n=25) in the first three minutes was 7±0.5±0.5 ml (SD), injection of sodium metabisulphite (n=15) caused no significant change (6±3±4.4 ml) whereas adrenaline (n=15) caused a significant decrease in the blood loss (2.9±1.9 ml, p<0.05). Conclusion: Submucosal adrenaline caused a decrease in the blood loss from artefactual ulcers. Endoscopic adrenaline injection may have a role to play in endoscopic haemostasis.

### Randomised controlled assessment of endoscopic adrenaline injection for actively bleeding ulcers

J W C LEUNG, S C S CHUNG, R J C STEEL, AND T J CROFTS (Combined Endoscopy Unit, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong) Sixty eight patients with actively bleeding (spurting or oozing) ulcers at emergency endoscopy were randomised to receive endoscopic adrenaline injection (aliquots of 0.5 ml of 1/10000 adrenaline up to a total of 10 ml) and no endoscopic treatment. The injection group comprised 34 patients (M=26, F=8; age 22–85, mean=51 years). nine had a spurt. In the control group (34 patients, M=26, F=8; age 17–86, mean=56 years). 10 had a spurt. After endoscopy both groups were given intravenous H2 blockers. Endoscopy was performed 24 hours later and injection repeated if necessary in the injection group. Strict criteria for emergency surgery were adhered to in both groups: (1) haemodynamic instability despite 4 units of blood, (2) total transfusion of eight units, or (3) rebleeding: haematemesis/red aspirate with tachycardia and/or hypotension. Initial haemostasis was achieved in 100% of injection group. The injection group required less blood transfusion (3±8±2.8 units v 5±9±5.4 units, p<0.05) and less emergency surgery (5 v 14, p<0.02) than the controls. There was no difference in mortality (3 v 2).

Endoscopic adrenaline injection is effective in stopping active ulcer bleeding. It significantly decreases transfusion and need for emergency surgery.

### Early blood transfusion promotes recurrent gastrointestinal haemorrhage

S D BLAIR, R M GREENHALGH (INTRODUCED BY R A PARKIN) (Departments of Surgery and Gastroenterology, Charing Cross and Westminster Medical School, London) It has been suggested that mortality caused by upper gastrointestinal haemorrhage may be reduced by restricting blood transfusion. We have assessed whether this is due to an anticoagulant effect in a prospective randomised trial.

One hundred patients with severe, acute gastrointestinal haemorrhage were randomised to receive either at least two units of blood during the first 24 hours of admission or no blood unless their haemoglobin was less than 8 g/dl or they were shocked. Minor bleeds and varices were excluded. As hypercoagulation cannot be measured using conventional coagulation tests, fresh whole blood coagulation was measured by the Biobridge Impedance Clotting Time (ICT) and the results expressed as mean±SEM. The ICT on admission for the transfusion group (n=50) was 4.4±0.3 mins (normal range 8–12 mins). This hypercoagulable state was partially reversed by early blood transfusion to 6.4±0.3 mins at 24 hours (p<0.001). The 50 allocated to receive no blood had a similar ICT on admission of
4.7±0.4 mins but the hypercoagulable state was maintained with ICT at 24 hours of 4.3±0.4 mins. Only two patients not transfused rebled compared to 15 in the early transfusion group (p<0.001). Five patients died, and they were all in the early transfusion groups.

These findings show there is a hypercoagulable response to haemorrhage which is partially reversed by blood transfusion leading to rebleeding.

Laser doppler assessment of human gastric blood flow

P. M. Allen, I. Chesner, K. Wheatley, and M. Goldman (Departments of Surgery and Medicine, University of Birmingham, Birmingham) Necropsy injection studies have shown that the ulcer prone areas of the stomach and duodenum have fewer mucosal arterioles, but physiological evidence of poorer perfusion is lacking.

We have studied 19 patients, median age 70 (range 27-83) using the non-invasive Laser Doppler (LD) technique. Flux measurements were made during gastroscope under diazepam sedation, using the Pentflu, P2 instrument. Readings were made at 9 sites: distal oesophagus, proximal, mid- and distal stomach on greater and lesser curves, and pre- and post-pylorus.

In all cases, the stomach was macroscopic normal. Flux varied from 40±28 V (mean±SD arbitrary units of flow) in the antrum to a maximum of 92±35 V on the lesser curve. In the proximal stomach, the mean value at each site exceeded 70 V whereas none of the five distal gastric sites had a mean value above 56 V. Overall flux in the proximal stomach at 77.5±39.8 V was significantly greater than that of 48.5±31.2 V in the antrum and pylorus (p<0.001 Student's t test).

This in vivo study demonstrates marked regionality of blood flow in the stomach and duodenum, being least in the ulcer-prone areas.

Prospective study of the effect of partial gastrectomy with Billroth-II and Roux-en-Y anastomosis on serum pepsinogens

J. B. Jansen, P. N. A. Reu, I. Biemond, H. J. M. Hoosten, and C. R. W. Lamers (Dept Gastroenterology and Hepatology, University Hospital Leiden and Dept Surgery, CWZ, Nijmegen, The Netherlands) Subtotal gastrectomy is usually followed by mucosal atrophy of the gastric remnant. This atrophy may be caused by reflux gastritis or to a reduced trophic effect of gastrin on the gastric body mucosa. In order to differentiate between these mechanisms, we prospectively studied serum concentrations of pepsinogens A (PgA) and C (PgC) before and 10 days, 1/2 year, and one year after subtotal gastrectomy in 22 patients. 11 of them randomly selected for Billroth II and 11 for Roux-en-Y anastomosis. Serum PgA and PgC levels were measured by radioimmunoassay.

Fasting bile acid reflux was increased from 1.0±0.5 mmol/l before to 12.1±4.75 mmol/l after Billroth II resection (p=0.01), but was reduced by the Roux-en-Y procedure from 0.6±0.4 mmol/l to 0.1±0.1 mmol/l (p=0.02). Serum PgA showed a progressive reduction with time, independent of the type of surgery; 115.5±6 V1 before and 87.13±12.1 V1 10 days (p<0.05), 75.10±12.1 V1 1/2 year (p<0.05), and 39.6±12.1 V1 one year (p<0.01) after Billroth II resection, and 95.8±2.1 V1 before and 67±8 V1 10 days (p<0.05), 53.2±8 V1 1/2 year (p<0.05), and 20±2 V1 one year (p<0.01) after Roux-en-Y surgery. There were no significant differences between the two groups of patients. Serum PgC levels remained unchanged and the serum PgA/PgC ratio was reduced in parallel with the reductions in serum PgA.

This study reveals a progressive decrease in serum PgA after gastrectomy, indicating progressive mucosal atrophy of the gastric remnant. As this decrease in serum PgA could not be precluded by prevention of enterogastric reflux by Roux-en-Y anastomosis, we suggest that this atrophy results from a reduced trophic action of gastrin because of the removal of the antrum.

Diagnosis of occult intra-abdominal sepsis with 111Indium labelled leucocyte scanning (ILS) - early versus late scanning

Sarah Cheshire, C. J. Barber, M. C. Aldridge, D. A. Cunningham, and H. A. D. Dudley (Academic Surgical Unit and Department of Radiology, St Mary's Hospital, London) Intra-abdominal sepsis remains a major cause of morbidity and mortality in surgical patients. 111Indium labelled leucocyte scanning is an established method of diagnosing occult sepsis but its major disadvantage compared with ultrasound or computed tomography is the significant delay before a result is obtained. This has been reduced by faster labelling methods but pure granulocyte preparations are advocated when the white cell count (WCC) is normal (<12x10/L). The importance of the early scan (three to four hours) and the use of mixed leucocyte preparations in patients without a leucocytosis has not been established. We have evaluated 101 scans in 81 patients with suspected intra-abdominal sepsis to assess (a) the diagnostic accuracy of the early scan (three to five hours) and (b) the relationship of the blood leucocyte count to the sensitivity of ILS. The positivity of ILS was confirmed by operation or spontaneous discharge of pus and negativity by recovery of the patient without further surgery.

In only four of 73 patients with both early and late scans was interpretation altered by the late scan. Twenty two of 23 scans in patients with a normal WCC were confirmed clinically but with a WCC of >20x10/L five of 30 scans were equivocal or gave false results.

It is concluded that the early scan is diagnostic in most cases but if it is negative or equivocal late scanning is recommended. A normal WCC does not exclude the use of this investigation and special preparation methods are not needed. Very high WBCs can be paradoxically associated with diagnostically inaccurate scans.

Impaired gastric adaptive relaxation in patients with postvagotomy diarrhoea

M. N. Hartley and C. R. Mackie (University Department of Surgery, Royal Liverpool Hospital, Liverpool) Gastric adaptive relaxation (GAR) is said to be impaired after truncal vagotomy and drainage (TV + D). Loss of GAR after vagotomy may contribute to the excessively rapid gastric emptying exhibited by patients with postvagotomy diarrhoea. We studied GAR in 10 healthy subjects (mean age 29 years, range 22–40), and 17 patients, six months to 17 years after TV + D (mean age 54 years, range 39–65 years) of whom six patients had persistent postvagotomy diarrhoea.

Fasted subjects were intubated with a Ryle's tube with a flaccid plastic bag (800 ml) attached and containing a pressure microtransducer. Gastric corpus-fundus pressure was recorded during distension of the bag with 460±30 ml (mean±SD) of air over 30 sec. Pressure indices (PI) were derived (area under curve: mean of four readings) and compared.

PI cmH2O (mean±SD) were: Controls 11.7±3.0 v TV + D (without diarrhoea) 15.4±2.2 v TV + D (with diarrhoea) 21.2±3.6 (p<0.01 ANOVA). This confirms GAR is significantly impaired in the patients...
impaired after TV+D and the degree of impairment is significantly greater in patients with diarrhoea than without.

Highly selective vagotomy (HSV) in the treatment of acute complications of peptic ulcer

M Rogers, D Johnston, J N Primrose, D C Ward, R I Blackett, and M J McMahon (University Department of Surgery, The General Infirmary, Leeds) Since the advent of the H$_2$-receptor antagonists, elective surgery for peptic ulcer (PU) has become less common. The complications of PU, however, continue unabated.

Highly selective vagotomy is the best elective surgical treatment for PU but what proportion of patients with acute complications can be treated with HSV, and how effective is it in curing the ulcer? These are vicious ulcers and one might expect the incidence of recurrent ulcer (RU) to be higher after HSV for complicated PU than after elective HSV for PU.

Since 1969, 985 patients have undergone HSV in this department of whom 127 (13%) underwent HSV for acute complications of PU (perforation = 70, haemorrhage = 57). Highly selective vagotomy was used in 33% of perforated PU's and 45% of bleeding PU's. Overall mortality was 1% (perforated PU 0%, bleeding PU 2%). Incidence of RU was 13% for perforated PU's, 2% for bleeding PU's (overall 8%) – no different from electively treated PU. Visick gradings were not significantly different from patients with PU's treated with elective HSV. In conclusion, HSV can be used in patients with acute complications of PU, and with careful case selection it carries a low mortality, low risk of RU and gives a good quality of life.

Clinical results 10 years after proximal gastric vagotomy

C Muller, R Teichmann, P Verreit, B Husemann, I Fiedler, and B Engler (Introduced by J H Baron) (Dept of Surgery, Kantonsspital, CH-4031 Basel, Switzerland) To assess long term results of proximal gastric vagotomy (PGV) sufficient numbers of patients actually followed-up for 10 years or more are needed. We report on a prospective multicentre trial on PGV initiated in 1974.

Between January 1974 and April 1975 717 patients underwent PGV: 524 for duodenal ulcer (DU), 94 for pyloric or prepyloric ulcer (PU/PPU), 71 for gastric ulcer type I (GU) and 28 for combined ulcers (GDU).

Complete follow up was achieved in 85-4%, 55% of which had routine endoscopy. Ten years' total recurrence rate (including asymptomatic recurrences) was 20-4% for DU, 32% for PU/PPU, 19-8% for GU and 31-7% for GDU. Complete vagotomy as assessed at operation by a modified Burge-Test significantly lowered the recurrence rate for DU to 13-6%. In PU/PPU a drainage procedure significantly improved the outcome (16-6% with versus 39% without drainage). At 10 years Visick grade I and II was found in 88% of the DU, 84% of the PU/PPU, 73% of the DU/PPU and 82% of the GDU.

The overall symptomatic result 10 years after PGV is good in all ulcer types. The chance of cure is 80% for DU and surprisingly for GU, but unsatisfactory for PU/PPU and GDU. The outcome is significantly improved by an intraoperative completeness test in DU and by a drainage procedure in PU/PPU.

Asbestos: a possible aetiological cause of gastric cancer?

P W Houghton, I Stewart, P Heap, N J M Mortensen, and R C N Williamson (Department of Surgery, Bristol Royal Infirmary and Department of Anatomy, University of Bristol, Bristol) There is some epidemiological evidence to suggest that workers exposed to asbestos have an excessive mortality from gastric cancer and it has been postulated that the high incidence of gastric cancer in Japan may be due to contamination of their polished rice by asbestos.

Scanning electron microscopy was performed on specimens of stomach taken from six patients with histologically proven gastric cancer and on three patients undergoing gastric resection for benign disease. In five of the six patients with gastric cancer unknown fibres were found in the tumour tissue and in one patient in the premalignant mucosa surrounding them. Simultaneous radiographic microanalysis of these fibres has shown them to contain silicon, magnesium, calcium and iron and their molar ratios strongly mimic the known x-ray elemental profile of tremolite asbestos. No fibres have been identified in any of the control tissue.

These findings suggest that mineral fibres might play an important role in the pathogenesis of gastric cancer.

A randomised, controlled study of adjuvant Tamoxifen in the treatment of gastric carcinoma

J D Harrison, D L Morris, J O Ellis, J Jones, and J Jackson (Department of Surgery, University Hospital, Nottingham) To investigate the effect of Tamoxifen in patients with gastric cancer. 100 patients were randomised after stratification to treatment or control groups. The treatment group received 40 mg Tamoxifen daily and the patients were followed up until death. The median survival in men was 25.5 weeks in the control group and 15.5 weeks in the treatment group, whilst amongst the women, the median survival in both groups was 25 weeks. To investigate the effect of oestrogen receptors on prognosis these patients' tumours had oestrogen receptor status measured. The overall cumulative survival in patients who were oestrogen receptor negative (ER−) was significantly better than in those patients whose tumours expressed oestrogen receptors (ER+), particularly in the female group. The median survival in ER+ women was 18.5 weeks compared to 33 weeks in the ER− women (Logrank test p<0.001). The median survival in men was 20 weeks for ER+ patients and 22 weeks for ER−. These studies show that the presence of oestrogen receptors in gastric carcinoma is an indicator of poor prognosis in women, and suggest that sex hormone manipulation in men may play a role in the treatment of gastric carcinoma.

C-myc oncogene product expression in benign and malignant gastric epithelia

W H Allan, K M Newbold, F MacDonald, B Russell, and H J Stokes (Introduced by M R Keighley) (Surgical Immunology Unit and Department of Pathology, Queen Elizabeth Hospital, Edgbaston, Birmingham) Amplification of the C-myc oncogene has been described in gastric cancer. In this study the expression of the oncogene product, p62 C-myc, has been assessed in both benign and malignant gastric epithelia to determine whether C-myc is important in gastric neoplasia. Histological sections of a range of benign and malignant epithelia have been examined in an immunohistochemical assay using a monoclonal antibody to p62 C-myc. In the benign tissue, staining was cytoplasmic. All tissue types showed some staining but gastritis was more commonly positive than normal epithelium. This was particularly marked in atrophic
gastritis showing type 2b intestinal metaplasia. There was no difference between active and quiescent chronic superficial gastritis suggesting that staining was not simply demonstrating proliferation. In a significant proportion staining was limited to the tips of the mucosal folds, sites not usually considered to be actively dividing. This was most marked in type 2b intestinal metaplasia. In tumours, less than 40% of specimens stained positively. When present staining was unrelated to differentiation, although there was a suggestion of increased positivity in intestinal type lesions. C-myc may be important in the progression to gastric malignancy and may regress once malignant change has occurred.

Use of CA-50 in the differential diagnosis of benign and malignant diseases of the stomach and oesophagus

S B KELLY, M J HERSHMAN, N A HARR, R C N WILLIAMSON, J SPENCER, AND C B WOOD (University Department of Surgery, Bristol Royal Infirmary, Royal and Department of Surgery, Royal Postgraduate Medical School, London) This study investigated the role of the tumour marker CA-50 (carcinoma associated antigen) in the differential diagnosis of benign and malignant diseases of the stomach and oesophagus. Serum was collected from 50 controls, 19 with benign oesophagogastroduodenal disease, 24 with gastric carcinoma, and 21 with oesophageal carcinoma. A radioimmunoassay (RIA) was used to detect CA-50 in the serum and a level of 17 units/ml was used as a cut-off between benign and malignant disease. All 50 normal subjects and 18 of 19 (95%) with benign oesophagogastroduodenal disease had CA-50 levels below 17 units/ml. In the cancer groups, 18 or 24 (75%) with gastric carcinoma and 15 of 21 (71%) with oesophageal carcinoma had CA-50 levels above 17 units/ml. Therefore, the sensitivity is 73% (33 of 45) and the specificity is 100% (50 of 50) and 95% (18 of 19) for the control and benign groups respectively. In patients with tumours and values above 17 units/ml, the mean concentration of serum CA-50 was 65±33 (range 31-132) for the gastric carcinomas and 58±30 (range 19-116) for the oesophageal carcinomas. These data suggest that the CA-50 RIA test could be of use in the differential diagnosis of benign and malignant diseases of the stomach and oesophagus.

Analysis of dyspeptic symptoms to determine risk of gastric cancer and priority for endoscopy

E M CHISHOLM, B J UNWIN, A G MORGAN, AND G R GILES (St James's Hospital, Leeds and Airedale Hospital, Keighley, Yorks) Screening for early gastric cancer (EGC) by gastroscopy in all middle-aged patients with a two week history of dyspepsia has recently been advocated. Unfortunately a 2-4% yield of cancer with a 98% false positive rate arose. We have attempted to further define risk of cancer and therefore priority for endoscopy in dyspeptic patients by analysis of their symptoms.

The relative incidence of symptoms in 100 patients with gastric cancer (20 EGC), 164 with benign upper gastrointestinal conditions and also in 300 middle-aged random population controls were recorded. A simple scoring index was then produced by applying the Log Likelihood Ratio statistic to these symptom frequencies to predict 'high risk' of cancer (defined as probability >0.05). Eighty one cancer patients were above this value with only a 6% false positive rate, giving a 74% yield for cancer.

To determine its clinical significance, the scoring index was recorded in 300 consecutive dyspeptic patients and was compared with a clinicians evaluation of cancer risk. Fifteen of 16 gastric cancers (4/4 EGC) were predicted by the index but only 9/16 were felt to have cancer by the clinician. The sensitivity, specificity and yield for cancer by the index compares well with the clinician's.

A simple risk index for gastric cancer using symptom analysis can predict cancer risk as accurately as a clinician, with a high yield per endoscopy, and may therefore be a useful aid in determining priority for endoscopy when screening for EGC.

Ability of duodenum to maintain a neutral pH microclimate in response to acid challenge in endoscopically normal and duodenal ulcer subjects

B J Z DANESI, O STARK, J M RAWLINGS, M I LUCAS, AND R I RUSSELL (Gastroenterology Unit, the Royal Infirmary and Department of Physiology, University of Glasgow, Glasgow) It has recently been shown in man that gastroduodenal mucosal surface is lined by a near-neutral pH microclimate. We measured duodenal mucosal surface pH on direct acid challenge in 11 endoscopically normal subjects (controls) and in 11 patients with active duodenal ulceration (DU). Using a pH electrode introduced through an endoscope, mucosal and luminal pH was measured in situ in the fundus, antrum, duodenal cap and loop before and during perfusion with phosphate (pH 1·5) buffer. Before acid perfusion, the duodenal mucosal pH was higher (p<0.001) in DU (7·2±0·1) than in controls (6·8±0·1). Despite comparable fundal luminal acidity in controls (2±4±0·5) and DU (1·8±0·1), luminal pH was more alkaline (p<0.05) in the duodenal loop in DU (7·4±0·2) than in the controls (7·4±0·2). Acid perfusion reduced (p<0.001) mucosal pH in the antrum, duodenal cap and loop in DU (ΔpH=1·1±0·4, 1·3±0·3, 1·1±0·2) but not in controls (ΔpH=0·2±0·1, 0·07±0·08, 0·1±0·4). During acid perfusion, mucosal pH was lower (p<0.01) in the duodenal cap and loop in DU patients (5·8±0·3, 6±0·1) than in the controls (6·8±0·1, 6·7±0·1).

The mucosal alkalinity observed in DU, not maintained during acid challenge, suggests that mucosal bicarbonate secretion is at a maximum drive in DU and the capacity to neutralise fully an acid surge seems limited.

Increased formation of leukotriene C4 (LTC4) in campylobacter pyloridis (CP) - associated gastritis

A AHMED, D VAIRA, S R CARNES, J HOLTON, M FILZON, A POLYDORUS, AND P R SALMON (Dept Gastroenterology, Microbiology, Histopathology, The Middlesex Hospital, London) The presence of CP in the gastric mucosa may be associated with inflammatory cell infiltration and consequent alteration in LTC4 and prostaglandin (PG) E2 levels which could play a proinflammatory role.

Antral biopsies of 13 dyspeptic patients were incubated at 37°C in pre-warmed/oxygenated Tyrode solution (basal release) and transferred to second incubation medium containing ionophore A23187 8 μg/ml (stimulated release). Supernatant leukotrienes were measured by radioimmunoassay.

Eight patients had acute gastritis (antral CP present in all) and five had normal antral histology (no evidence of CP).

Basal release (pg/mgww/20 min, means±SE) of LTC4 and PGE2 in normal (74±11±3 and 1691±336-2) and abnormal mucosa (94±14±2 and 182±330-3) were similar. Stimulated release of LTC4 (147±21-1) was significantly enhanced com-
pared to basal levels in gastritis (p<0.05). Stimulated LTC4 in abnormal mucosa was significantly greater than normal mucosa (81±9.2, p<0.05). Basal and stimulated PGE2 levels in normal versus abnormal mucosa were similar.

These results suggest that LTC4 formation may be of greater importance than PGE2 synthesis in CP associated acute gastritis probably reflecting inflammatory cell infiltrate.

**Comparative study of 4-hour rapid urease test (RUT) to culture and histology for the detection of Campylobacter pyloridis (CP) in gastric and duodenal biopsies**

D VAIRA, J HOLT, M MALZON, A AHMED, S R CAIRNS, and P R SALMON (Dept of Gastroenterology, Microbiology, Histopathology, Middlesex Hospital, London) The clinical significance of CP in gastroduodenal biopsies is uncertain. The aim of this study was to evaluate the sensitivity and specificity of the four-hour RUT to histology and CP culture in the detection of CP in gastroduodenal biopsies.

Gastric and duodenal biopsies from 24 dyspeptic patients were homogenised in 0.9% saline and immersed in 2% urea broth.

Biopsies from 16 patients (66.6%) showed evidence of gastritis and/or duodenitis, despite 5 showing no macroscopical abnormality. All these 16 patients showed CP on histology, indicating a high correlation between the presence of CP and acute gastric and/or duodenal inflammation.

Determination of the sensitivity for RUT to histology and culture was 81.3%, 56.3% and specificity was 100% and 100% respectively.

This study shows: (1) Even when no macroscopic abnormality is found at endoscopy of dyspeptic patients histology and four-hour RUT may reveal antral CP. (2) The four-hour RUT can provide a rapid and useful method for the assessment of acute gastritis and/or duodenitis in dyspeptic patients.

**Smoking and pH-response to H2-receptor antagonists**

C-C SCHUERMANN, I VARGA, H R KOELZ, and F HALTER (Gastrointestinal Unit, University Hospital, Inselspital, Bern and Gastrointestinal Unit, Triemlsipital, Zürich, Switzerland) Smoking has been shown to impair the effect of H2-receptor antagonists. To evaluate onset and duration of H2-receptor antagonist action in relation to smoking habits, we tested the effect of ranitidine (RAN) and famotidine (FAM) under physiological conditions, using ambulatory pH-metry. Intragastric pH was measured over 20 hours. Each of 18 healthy volunteers, 20–36 years, nine smokers and nine, age and sex matched non-smokers, received either 40 mg FAM, 300 mg RAN or Placebo in a double blind, randomised study as a single evening dose, 18.00. With both drugs 20 hours acidity was markedly suppressed. After FAM treatment mean inhibition in smokers was 42%, in non-smokers 76%, with RAN 60% and 67% respectively. When areas under the pH-curves from each individual were calculated and treatment compared to placebo (=100%), with either drug response was smaller in smokers than in non-smokers (FAM 153±21% versus 214±19%, p<0.01, RAN 176±21% versus 232±29%, p<0.05) during the first four hours after drug intake. A similar effect was observed in the morning period from 6–1000 (FAM 118±19% versus 206±19%, p<0.001, RAN 133±21% versus 207±31%, p<0.02). During night time there were no significant differences.

These results indicate that smoking impairs onset and duration of response of both drugs tested.

**Smoking delays gastric emptying of solids**

G MILLER, C FARRINGTON, V SMITH, M V MERRICK, and K R PALMER (Departments of Nuclear Medicine and the Gastrointestinal Unit, Western General Hospital, Edinburgh) The effects of smoking upon oesophagogastric transit were defined in eight healthy volunteers by radionuclide scanning an ingested test meal. Oesophageal clearance was measured by examining three areas of interest during a liquid swallow of In111 labelled water and during a semisolid swallow of Tc99m labelled omelette. Gastric emptying of the swallowed test meal was then measured by a standard double counting technique. Finally vallasalva and postural manoeuvres were used in an attempt to provide gastro-oesophageal reflux (GOR). Each subject was studied under basal conditions, whilst continuously smoking and then whilst chewing nicotine gum.

Oesophageal transit was unaffected by smoking or gum (mean basal liquid transit 7.5±1.1 (SEM) smoking 6.6±1.1 gum 6.3±1.1 sec). Gastric liquid emptying was exponential and unaffected by smoking or gum T1/2 20±6.2±3, 21±4.7±3, 13±6.2±1 mins). Gastric solid emptying had two components, both of which were prolonged by smoking but not gum. An initial lag phase (mean basal, 18±4.2±7, smoking, 28±5.7 (p<0.05), gum 18±3±3 mins) and a subsequent linear emptying phase (mean basal 1.07±0.13, smoking 0.85±0.09 (p<0.05), gum 0.98±0.49%/(min). No episodes of GOR were observed.

Gastro-oesophageal reflux is associated with delayed solid but not liquid emptying and our findings suggest a mechanism for the observation that smoking exacerbates symptoms in susceptible individuals.

**Mucosal repair of rabbit duodenum: role of an alkaline micro-environment**

W FEHL, P KARNER, S KLIMESCH, M STARLINGER, and R SCHIESSEL (INTRODUCED BY A GARNER) (Surgical Dept 1, Univ Clinic of Vienna, A-1090 Vienna, Austria) The duodenal mucosa of the rabbit has the ability to repair itself rapidly after acid injury. In this study we investigated the importance of nutrient bicarbonate and of the layer of necrotic tissue (=alkaline micro-environment) for the repair process after acid damage.

Mucosal sheets of rabbit duodenum mounted in Ussing-chambers were exposed to 10 mM luminal acid for 10 min. After injury the luminal saline solution was either adjusted to pH1 7.4 or pH1 7 and the nutrient solution contained either 25 mM HCO3 or HEPES. In some experiments the necrotic layer was removed by scraping (RN). Tissues were allowed to recover five hours after injury. We measured: alkaline secretion (AS), potential difference (PD), and performed histology.

Acid exposure caused a 67% drop in PD (from 2.9 to 0.9 mV), a 28% increase of AS (from 0.67 to 0.86 μEq/cm2–10 min) and damage of 95% of villi (n=48). After five hours morphometry showed repair of 72% of villi (HCO3→, pH1→7.4, 52% (HCO3→, pH1→3), 69% (HEPES, pH1→7.4), 0% (HEPES, pH1→3), 52% (HCO3→, pH1→7.4, RN) and 27% (HCO3→, pH1→3, RN) respectively (n=8, each group).

The absence of nutrient HCO3 did not impair the repair process at pH1→7.4 but at pH1→3. RN delayed repair at pH1→7.4 but prevented this process almost completely at pH1→3. We conclude, that mucosal repair in the duodenum is dependent on the presence of the necrotic layer and the availability of nutrient HCO3.−
Synthetic secretin secretolin (SS): an adequate substitute to GIH natural secretin (NS) for secretin provocation test in Zollinger-Ellison syndrome (ZES)

M Mignon, I Elouaer-Blanc, D Riaud, P Ruszniewski, T Chevalier, T Valiot, J Latier, E Rien, and M Due (Service de Gastroenterologie, Hopital Bichat, Paris and Laboratoire de Radioimmunologie, Hopital Lariboisiere, Paris, France)

Synthetic secretin secretolin is equipotent to NS on gastric release in control and duodenal ulcer (DU) subjects (1987) but the comparative efficacy of SS for ZES diagnosis was not assessed. As GIH NS will no longer be available, both Höechst SS and NS effects on acid, gastrin secretion were evaluated in 10 unoperated ZES (53±13 years) and 13 DU (43±16 years). In randomised sequences 3 CU/kg SS and NS were infused for one hour after antiseptic drugs withdrawal for three days. Serum gastrin (SG, pg/ml), acid output (AO, mmol/h) were measured simultaneously: four SG samples and one hour AO were obtained before and upon secretin infusion. Parametric or non parametric paired-data analysis was used according to results distribution. In ZES: basal AO (BAO) was 25±11; AO rose more on SS (AO; 35±4±15) than on NS (AO; 31±8±16); difference BAO versus (v) AOS and AOSS v AONS: p<0.05. Basal SG (BSG) was 219 (84-7813) and increased more on SS (SG: 959, 118-18769) than on NS (SG: 34, 92-1218N); difference BSG v SGSS and SGSS v SGNS: p<0.05. In DU: BAO was 9-7±5; AO decreased more on SS (AO: 0-57±1-1) than on NS (AO: 1-28±1-25); difference BAO v AOS or AONS: p<0.001. Difference AOS v AONS: p<0.005. SG was unchanged by both SS and NS. Thus compared to NS, SS induced higher inhibition of AO in DU, higher increase in AO and SG in ZES and can be confidently substituted to NS for ZES screening. *(M±SD)

Human antropyloroduodenal motor activity after intraduodenal acid infusion

D D Kerrigan, I A Houghton, N W Read, and A G Johnson (Dept of Surgery and Sub-Dept of Human Gastrointestinal Physiology and Nutrition, University of Sheffield, Sheffield)

A manometric catheter was used to record pressure activity in the antrum (three sites), pylorus and duodenum (four sites) in 12 healthy fasted volunteers during intraduodenal infusion of normal saline and isotonic 0-1 M HCl. Pyloric pressure was recorded using a 4 cm long sleeve sensor positioned by measuring the transmucosal PD at either end of the sleeve. Intraluminal pH was measured in the terminal antrum and at two positions in the proximal duodenum. Saline and acid were infused into the duodenal bulb alternately for consecutive 30 minute periods for up to three hours at both 1 and 2 ml/min. During acid infusion there was (1) a significant reduction in the frequency of antral pressure waves [acid, 8h (0-54h) median (range); saline, 87h (10-272h)]: p<0.01; (2) a marked increase in pressure waves confined to the pylorus [acid, 18h (6-128h)]: saline, 2h (0-14h); p<0.01); (3) a reduction of coordinated pressure waves involving the duodenum [acid, 13h (0-50h)]: saline, 45h (24-70h): p<0.01. These changes were reversed during subsequent saline infusion but returned during the next acid infusion. Thus our data indicates that acidification of the duodenum may slow gastric emptying by causing reproducible reversible inhibition of antral pressure activity, increasing pyloric resistance and reducing duodenal coordination.

Reproducibility of 24-hour studies of intra-gastric acidity, nocturnal volume, acid and pepsin secretion by the aspiration method

M Deakin and J G Williams (Department of Gastroenterology, Royal Naval Hospital Haslar, Portsmouth, Hants) Whilst 24 hour study techniques have been widely used in the evaluation of antisecretory drugs there has been no previous formal assessment of reproducibility. Eight volunteers with duodenal ulcers in remission were studied during two 24 hour periods using a size 10 French sump type nasogastric tube. Three standard meals of 375 ml of clinified with one Oxo cube in 200 ml of hot water were taken during each 24 hour period at 0800, 1300, and 1800 hrs. Gastric aspirates were taken for pH recording at 15 minutes after each meal for three hours and half hourly between meals. During the night the stomach was kept empty by a continuous, intermittent positive pressure, aspiration pump. The intragastric pH profiles were virtually identical on both days in all eight subjects. For each patient pH scores for the 24 hour period varied by 6-8% (0-21%); median (range). Nocturnal volume, acid and pepsin secretion were more variable. Median percentage differences between days 1 and 2 were: acid output 36% (2-661%): pepsin output 80% (35-210%); pepsin concentration 41% (0-93%) and volume output 50% (5-153%).

Intragastrectic pH is the most reproducible and most convenient parameter for the study of a drug effect. Outputs are more variable making measurements for an individual patient unreliable.

Effect of meal temperature on gastric emptying of liquids in man

W M Sun, I A Houghton, N W Read, D Grundy, and A G Johnson (Dept of Surgery and Sub-Dept of Human Gastrointestinal Physiology and Nutrition, University of Sheffield, Sheffield) The existence of thermoreceptors, responding to temperatures of 10-12°C and 46-49°C in the mucosa of the stomach and duodenum suggests the
possibility that the temperature of food may influence the rate of gastric emptying. Intra-
gastric temperature from two sites and gastric emptying rates were measured con-
tinuously in six normal volunteers after ingestion of 400 ml radiolabelled orange
juice at either 50, 37, or 4°C. The highest
(43±0.4°C, mean±SEM) and the lowest
(21±2.1°C) intragastric temperatures
occurred within a minute of ingestion, then
returning to body temperature within 20
minutes. Differences in intragastric
temperature between the warm and control
drink were significant up to six minutes and
between the cold and control up to 10
minutes after ingestion (p<0.05). The
initial rate of gastric emptying of the cold
drink was significantly slower than the con-
trol; at 10 minutes 76±7% of the cold drink
and 59±4% (p<0.05) of the control drink
remained in the stomach. The difference in
emptying rates between the cold and control
drinks were significantly correlated with
differences in intragastric temperatures
(r=0.98; p<0.01). Initial emptying of the
warm drink also appeared slow, was not
significantly different compared with con-
trol. Thus our data indicated that meal
temperature effects the rate of gastric
emptying when intragastric temperature differs from body temperature.

Validation of non-invasive assessment of
duodenogastric reflux (DGR)

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KING, AND M C J BARKER (University Depart-
ment of Surgery and the Department of
Nuclear Medicine, The General Infirmary,
Leeds) Duodeno gastric reflux has traditionally
been investigated by studying gastric con-
tent aspirated through a nasogastric
tube (NGT). The NGT may itself, however,
affect DGR. Although well counting of
gastric aspirate after administration of
THa-EHIDA has been compared with bile
acid concentration (BAC) in gastric aspirate,
external gamma camera imaging after
THa-EHIDA has not been compared with traditional methods involving a NGT.

We studied DGR both by THa-EHIDA/
external imaging (DGR-HIDA) and by
estimation of BAC in gastric aspirate
(DGR-NGT) in the same 48 patients. In
seven, the reproductibility of DGR-HIDA
was studied by repeat imaging after 48–72
hours. In a further seven subjects imaging
was repeated after 48–72 hours, but with a
nasogastric tube in situ.

DGR-HIDA in the second test did not
differ significantly from DGR-HIDA in the
first test (p=NS, r=0.65). The presence of
NGT did not affect DGR significantly.
DGR-HIDA was found to correlate
significantly with DGR-NGT (p<0.001 for
both peak and post prandial DGR). When
DGR-HIDA and DGR-NGT were measured simultaneously correlation was
excellent (r=0.88, p<0.01).

Thus THa-EHIDA/external imaging provides a convenient and reliable method
for measuring duodenogastric reflux.

Value of the alkali infusion test in the
diagnosis of reflux gastritis

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CORSTENS (Dept Gastroenterology, University Hospital Leiden and Dept
Gastroenterology and Nuclear Medicine, St
Radboud Hospital, Nijmegen, The Nether-
lands) The diagnosis of alkaline reflux
gastritis is based on clinical (post-prandial
pain, bilious vomiting, weight loss), endo-
scopical and histological findings. These
criteria, however, do not allow to reliably
select patients for surgical treatment. The
alkali provoked test has been reported to be
a simple, safe and reliable diagnostic
test. To determine the value of this test we
have compared the results of this subjective

test with the quantitative measurement of
terogastric reflux of THa-HIDA in 16
patients (11 M, 14 postgastrectomy; age
35–63 yr) with clinical, endoscopical and
histological findings suggestive of reflux
gastritis. The alkali provocation test was
performed by intragastric infusion in
random order of 20 ml saline, 20 ml 1-M
NaOH, and 20 ml 0.1 M HCl separated by
10 min periods. The tests were done single
blind and were considered to be positive if
typical complaints were experienced during
infusion of 0.1 M NaOH, but not during 0.1
M HCl and saline. To determine the repro-
ducibility of the test, all infusions were
given twice. In the THa-HIDA test 3 mCi
was injected intravenously and gall bladder
eemptying was stimulated by oral ingestion
of 60 ml corn oil.

A positive alkali infusion test was found
in nine of 10 patients with an increased
terogastric reflux index of more than 10%
and in two of six patients with a normal
index (p<0.05), giving an overall agree-
ment of 81%. The tests were fully repro-
ducible in 10, partly reproducible in four and
irreproducible in two patients. Four of the
patients with a positive alkali infusion test
had negative tests when tested after
Roux-en-Y surgery.

The alkali infusion test, a simple,
inexpensive and safe test for the diagnosis
of alkaline reflux gastritis, shows good

correlation with measurement of enterog-


Gastric and duodenal subnuclear vacuolated
mucous cells

I W THOMPSON, D W DAY, AND N A WRIGHT
(Departments of Pathology, Royal Post-
graduate Medical School, Hammersmith
Hospital and University Department of
Pathology, Royal Liverpool Hospital,
Liverpool) We report a novel abnormality
affecting small mucin secreting cells
(SMC) of the glands of pyloric gastric
mucosa and of Brunner’s glands. Sub-
nuclear vacuolated mucous cells (SMVC)
show a distinctive appearance of haema-
toxylin and cosin staining. They are
columnar cells of similar size to SMC, but
have a central nucleus beneath which the
cyttoplasm has a uniform ‘glassy’ cosmo-
philic appearance or contains a clear area.

Subnuclear vacuolated mucous cells are
found focally lining the lower third of
pyloric gastric glands or in Brunner’s
glands, and may be mistaken for a form of
metaplasia. Histochemically, the apical
portion of the cell stains for neutral mucin,
but the basal portion stains only weakly and
differently, variably for protein. Electron
microscopy reveals that the basal portion consists of a
large, single, membrane bound vacuole,
variably indented by the nucleus, and prob-
bly derived from either endoplasmic
reticulum or the Golgi apparatus. The
vacuole contains granular material which
varies in electron density from cell to cell.
The apical portion of the cell contains organelles similar to SMC. These
appearances are highly suggestive of an abnormal
accumulation of non-glycoconjugated
mucous core protein. Although the cause
of this is unknown, it was associated with the
histological changes of chronic gastritis in 10
of our 12 cases.

A prospective study of Campylobacter
pyloridis by bacteriology, histology, urease

test, and serology (ELISA and immunoblot-
ing)

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ENDTZ, G J A OFFERHAUS, G DEN HARTOG, J
KRUUNING, AND C B H W LAMERS (Depts of
Gastroenterology and Hepatology, Pathology
and Microbiology, University Hospital
Leiden, The Netherlands) Patients
referred for upper GI endoscopy were
evaluated for the presence of Campylobacter pyloridis (CP) to determine the value of different tests in the diagnosis, using the bacteriological test as the gold standard.

Twenty six unslected patients were studied. Five antral biopsy specimens were taken for culture and bacteriological tests, histology (morphology and Warth and Starr (WS) staining), and urease test (120-180 min and 24 h). Serum antibodies against sonicated CP organisms were assayed by an ELISA IgA, IgG, and IgM as well as an IgG immunoblotting technique (IgG-IB).

Campylobacter pyloridis was found by culture in 50% of the patients and fulfilled the bacteriological criteria for CP. The WS staining and IgG-IB gave a sensitivity of 100% and a specificity of 85%, ELISA-IgG 85% and 91%, ELISA-IgA 46% and 85%, histological evidence of gastritis 92% and 54%, urease test (120-180 min) 70% and 100%, urease test (24 h) 92% and 54% as to sensitivity and specificity, respectively. No IgM anti-CP were detected in serum.

The WS staining technique and IgG-IB were the best techniques to detect the presence of CP, followed by ELISA-IgG. The urease test was less satisfactory. None of the patients but one with normal histology had a positive culture. Three patients with chronic antrum gastritis had a negative culture and WS staining but positive antibodies, thus suggesting, a possible aetiological role of CP in chronic antrum gastritis in addition to the well established CP role in acute antrum gastritis.

Gastric secretion of antibiotics used for Campylobacter pyloridis

J A HOLLINGSWORTH, J GOLDIE, C F SILLETTI, Y LI, H RICHARDSON, AND R H HUNT (McMaster University Medical Centre, Hamilton, Ontario, Canada) Erythromycin has a low rate of eradication of Campylobacter pyloridis (15%) while metronidazole and ampicillin esters are highly effective (85%). We have found C pyloridis difficult to eradicate from the gastric glands and postulate that while topically active agents may clear the organism initially early relapse may be associated with persistence in gastric pits. Gastric secretion of antibiotics should result in high drug concentrations in the gastric glands. Gastric juice levels of metronidazole and ampicillin were measured in four subjects in samples taken one hour before and two hours after the drug were given intravenously. Ampicillin was measured by bioassay and metronidazole by HPLC. No ampicillin was detected in any samples despite a mean serum level of 4-95 mcg/ml (sd 0.12). Peak metronidazole levels in gastric juice were 61 mg/ml (sd 8) at 30 mins and 30 mg/ml (sd 0.23) in serum at one hour.

These findings suggest that gastric secretion of antibiotics does not explain their varying efficacy in the eradication of C pyloridis. Other factors, such as luminal effects of oral antibiotics on gastric mucus and mucosa, and tissue levels may be more important.

In vitro mucus glycoprotein synthesis and secretion by gastric mucosa colonised with campylobacter pyloridis

J E CRABTREE, B J RATHBONE, J J WYATT, R V HEATLEY, AND M S LOSOWSKY (Dept of Medicine and Dept of Pathology, St James’s University Hospital, Leeds) There is a strong correlation between Campylobacter pyloridis colonisation and gastritis. The association between surface C pyloridis with depletion of neutral cytoplasmic mucins in the gastric epithelial cells raises the possibility that C pyloridis may be directly or indirectly affecting the protective mucus layer in the stomach. To study the capacity of normal and gastritic mucosa to synthesise and secrete mucus glycoproteins, 24 hour in vitro cultures of antral and body biopsies were undertaken. The incorporation of H glucosamine into tissue and secreted glycoproteins was measured (DPN×106/mg protein).

C pyloridis colonised antral biopsies secreted significantly higher quantities of labelled glycoproteins than normal antral tissue. Mean values respectively were 106±14-2 (n=6) and 58±7±9-8 (n=7) (p<0.05). Conversely, tissue associated labelled glycoproteins were higher in normal antral biopsies (198±19-2) than gastritic biopsies (159±15-5). Total incorporation of glucosamine into tissue and secreted glycoproteins was significantly greater (p<0.01) in C pyloridis infected body biopsies (258±19-2; n=7) than normal tissue (146±10-3; n=8). The increase in glycoprotein synthesis correlated with an increase in epithelial cell numbers (r=0.66, p<0.05). The ratios of tissue to secreted glycoproteins for normal and gastritic body tissue were 2:8:1 and 1:7:1 respectively.

These results show that in non-autoimmune gastritis where C pyloridis is present significant alterations to gastric mucus production occur. Whether the alterations in mucus production are a direct affect of C pyloridis remains to be determined.

Efficacy of different dosage regimes in duodenal ulcer healing and eradication of Campylobacter pylorid

J G COGHILL, D GILLIGAN, H HUMPHRYS, D MCKENNA, E SWEENEY, C KEANE, AND C O’MORAIN (Dept of Micro and Histopath, St James’ Hospital and Trinity College, Dept of Gastro, Meath/Adeleia Hospitals, Dublin, Ireland) Campylobacter pylorid (CP) status of patients with healed duodenal ulcers has recently been shown to be highly predictive of the likelihood of relapse. Colloidal bismuth subtricate (CBS) is active against CP in vivo. The aim of this prospective controlled trial was to assess the efficacy of CBS 120 mg qds v 240 mg bd in ulcer healing and CP eradication.

Sixty consecutive patients with endoscopic duodenal ulcers (DU) randomised (30 bd 30 qds CBS). Repeat endoscopy was performed at four weeks and again at eight weeks in patients who had not healed at four weeks. At each endoscopy two antral biopsies were taken from <2 cm from the pylorus and assessed histologically and microbiologically for evidence of CP.

At entry 90% of both groups were positive for CP, at four weeks 62% of bd and 33% of qds patients remained CP positive (p<0.05), at eight weeks 50% of bd patients and 16% of qds patients remained CP positive (p<0.02).

At the end of the study period there was no significant difference in healing rates between the groups (65% of bd and 75% of qds having healed).

Qds dosage reduces CP infection more effectively and should be associated with a lower DU relapse rate. Different mechanisms of action must operate in CP eradication and DU healing with CBS.

Campylobacter pylorid in tropical Africa

JUDITH I WYATT, J S DE CAESTECKER, B J RATHBONE, AND R V HEATLEY (Depts Pathology and Medicine, St James’s University Hospital, Leeds and Dept Medicine, University of Science and Technology, Kumasi, Ghana) Virtually all Campylobacter pylorid (CP) studies date to have concentrated on western style populations, yet in the tropics duodenal ulcers are reported to be particularly common and benign gastric ulcers rare. We studied the presence of CP, its relation to mucosal inflammation and patients serological responses in 39 patients being endoscoped in Kumasi, Ghana, West Africa. Histology was performed on antral, body, and duo-
denal biopsies including a modified Giemsa stain for identifying CP. Serum antibody titres to CP were studied by ELISA using a soluble antigen preparation. The patients mean age was 41 years (range 12–71) (male: female 28:11). The mean duration of abdominal symptoms was four years. Thirty eight of 39 patients had antral gastritis, and 23 of these (59%) had duodenal ulcer (14) or duodenitis (nine). The 38 gastric patients were all CP +ve, and the single normal subject –ve. The prevalence of CP colonisation in this African population is the highest reported in any study. The strong association with CP gastritis and duodenal disease seen in the Ghana patients is similar to that observed in the UK.

The effect of vagotomy on Campylobacter pylori

BELINDA J JOHNSTON, P J REED, AND M H ALI (Departments of Gastroenterology and Histopathology, Wexham Park Hospital, Slough, Berkshire) It is recognised that the gastritis seen in duodenal ulcer (DU) patients is associated with the presence of antral Campylobacter pylori (CP). It has been suggested that after gastric surgery the gastritis type will alter and may no longer be associated with CP presence.

To establish the existence of such a difference, gastric antral biopsies were taken from 61 patients who underwent vagotomy for DU, 1–20 years previously, and from 75 untreated patients with active DU. Of those who had surgery 27 had highly selective vagotomy (HSV), 26 vagotomy and pyloroplasty (VP) and eight truncal vagotomy and gastroenterostomy (TVGE). The biopsies were assessed histologically and examined for the presence of CP. Gastric juice pH was measured in the vagotomy patients.

Campylobacter pylori were present in 72 (96%) of the DU patients all of whom had histological gastritis. Forty four (71%) of the vagotomy patients were CP positive and 41 of these had histological gastritis (HSV 67%, VP 65%, and TVGE 75%), which tended to be more pronounced in the TVGE group. The severity of the gastritis was unrelated to the intragastric pH or time since surgery. Although the proportion of normal biopsies was higher in patients with vagotomy than with active DU, the gastritis in the former group was always associated with the presence of CP. These data would indicate that after vagotomy, the association between CP presence and gastritis is similar to that found in the unoperated DU stomach.

Non-invasive measurement of gastric emptying using applied potential tomography (APT)

D F EVANS, J W WRIGHT, G LAMONT, AND J D HARDCASTLE (Department of Surgery, University Hospital, Nottingham) Applied potential tomography is a new non-invasive technique which measures changes in tissue resistivity via surface electrodes. Gastric emptying of meals can be assessed using this method without the need for radioisotopes or expensive nuclear imaging equipment.

Five normal subjects were imaged on two occasions after ingestion of 500 ml Oxo drink and again after 500 ml of Quaker Oats porridge to assess liquid and solid emptying. Resistive images were collected at one minute intervals for 60 and 180 minutes respectively. The tests were repeated after 400 mg of cimetidine as gastric acid secretion is thought to influence imaging using APT.

The time taken to empty 50% of the test meals was expressed as t50. In the control studies t50 for the liquid meal was a median of 35 min (range 20–40 min) compared with t50 of 19 min (range 18–31 min) with cimetidine (p=0.028). For the solid meal t50 control was a median of 102 min (range 80–117 min) compared with t50 68 min (range 43–94 min) with cimetidine (p=0.016).

Applied potential tomography is a useful technique to evaluate gastric emptying and is particularly suitable when multiple investigations are required. Cimetidine does modify the emptying pattern and this should be considered for future studies.

Enterochromaffin like (ECL) cell populations are dependent on age and sex

A E BISHOP, D M GREEN, G RINDL, F I LEE, P J ISAACS, M J DALY, J DOMIN, S R BLOOM, AND J M POLAK (Depts of Histochemistry and Medicine, RPMs, Hammersmith Hospital, London, Dept of Pathology, Leeds General Infirmary, Leeds, Dept of Gastroenterology, Victoria Hospital, Blackpool, and Astra Pharmaceuticals, Edinburgh) To examine variations in ECL cells with age and sex, a two part, retrospective and prospective, study was made. Retrospectively, surgical and endoscopic biopsies, previously reported as normal although some had low grade gastritis, were taken from the files. Four groups of subjects were studied: men 45 (n=5) and 55 years (n=13) and similar female groups (n=5) and n=15. Prospectively, endoscopic biopsies were taken at standard sites from stomachs of selected subjects without gastritis (men 45, n=9, 55, n=10; women 45, n=11, 55, n=8) and plasma gastrin concentrations were measured. In the retrospective samples, the only significant change was a rise in ECL cells of older females (13±6±1.9, mean±SEM, cells/visual field) compared with the young group (10±6±0.8, p<0.03). The prospectively biopsied, however, selected subjects of both sexes showed reduced ECL cells with age (males 45, 50±10±6, 55, 55±3±6, p<0.05; females 45, 44±6±5, 55, 31±4±4, p<0.05). Gastrin concentrations did not change within sexes but were higher in older females (22±9±7 pmol/l) compared with older men (6±3±6±0, p<0.05). The difference in the two sets of results may reflect the high incidence of gastritis observed in non-selected older women. This in turn may relate to plasma gastrin concentrations which were relatively higher even in the selected group of older females. These variations should be taken into account when assessing pathological changes in ECL cells.

Duodenal acidification and gastrin responses after feeding: a new look at the pathophysiology

C A ERIKSEN, K D BUCHANAN, AND A CUCHERIERI (Department of Surgery, Ninewells Hospital and Medical School, Dundee and Dept of Medicine, Queen’s University of Belfast, Belfast) Controversy exists regarding the duodenal acidification and gastrin responses to sham feeding and a meal in ulcer disease. We measured plasma gastrin and duodenal bulb pH before, during, and after modified sham feeding (MSF) and a solid meal in 16 duodenal ulcer patients (12 DU) and 12 volunteers (VOL). Gastrin levels were significantly higher in DU than VOL (fasting: DU 42.5 ng/l, VOL 22.5 ng/l, p<0.001; meal peak: 130.0, 60.0, p<0.02). Two distinct DU groups emerged: ‘hypergastrinaemic’ (H’G) showed exaggerated gastrin responses; ‘normogastrinaemic’ (N’G) showed levels similar to controls. Cephalic stimulation produced significantly greater responses only in H’G (H’G fasting 67.7 ng/l, MSF peak 130.0 ng/l, p<0.05).

After the meal, both patient groups experienced significant delays in both, onset of duodenal acidity (H’G: 54.0 min, N’G: 89.5 min, VOL: 16.0 min, p<0.02), and time to peak acid response. H’G showed a prolonged duodenal acid exposure and returned to pre-meal pH levels significantly slower (H’G: 78.0 min, N’G: 28.0 min, p<0.05).
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These results show a 'hypergastrinemic' subset of DU patients, exhibiting marked cephalic responses, abnormal duodenal acidification and a defective switch off mechanism of acid secretion.

Evidence for a gastro-cholecystic reflex for gall bladder emptying in man

S ELLENBOGEN, J S GRIME, J CALAM, C R MACKIE, S A JENKINS, AND J N BAXTER (Department of Surgery, University of Liverpool, Department of Nuclear Medicine, Royal Liverpool Hospital, Department of Gastroenterology Royal PG Med School, London) A gastric phase of gall bladder emptying (GBE) has been demonstrated in the dog. In this study 'Te'-EHIDA cholecystigraphy was used to confirm its presence and mechanism of action in man. Healthy volunteers were studied; group I, no gastric distension (n=18); group II, gastric distension by balloon (n=9); group III, atropine given before gastric distension (n=7); group IV, meal ingestion (n=14). Gastric distension was also performed in patients with truncal vagotomy group V (n=9). Blood samples were taken for cholecystokinin bioassay. In group I, the probability of spontaneous GBE in any minute period was 0.0053. Significant GBE occurred in six of nine (66%) group II (p<0.001, group II v group I, Poisson Test), none of seven (0%) group III (p=0.0144, group III v group II, Fisher’s Exact Test). 14 of 14 (100%) group IV, four of nine (44%) group V (p=0.6372, group V v group II, Fisher’s Exact Test). From the start of gastric distension, onset of GBE was 8.2±1.9 minutes group II, 11.9±2.6 minutes group IV, 4.8±1.1 minutes group VI. From the start of GBE, 20 minute gall bladder ejection fraction was 41.0±6.9% group II, 29.2±5.3% group IV, 32.2±5.8% group V. Plasma cholecystokinin did not rise significantly from basal following gastric distension. These results suggest that a gastric phase of GBE exists in man, which persists after truncal vagotomy but is inhibited by atropine and independent of cholecystokinin.

The ‘acid antrum’ as a possible cause of recurrent ulceration after highly selective vagotomy (HSV): a histological study

K S NAIK, M LAGOPOULOS, J N PRIMROSE, AND D JOHNSTON (University Departments of Surgery and Anatomy, The University, Leeds and Leeds General Infirmary, Leeds)

The aim of this study was to standardise the definition of the antrum in terms of the macroscopic antrum – corpus boundary defined by the nerve of Latarjet (NL-ACB) and microscopical ACB according to both parietal cells (PC) and gastrin cells (GC), and hence determine if HSV provides reliable derervation of the distal PC mass. Serial sections obtained from longitudinal strips of 43 human ‘normal’ post-mortem stomachs were stained for PC (43 stomachs) and GC (in 20 of the 43). The PC-ACB was distal to NL by more than 1 cm in 26 stomachs (61%). In seven stools (16%) PC extended to the pylorus (‘acid antrum’). Of the 20 stomachs stained for GC and PC, extended to the pylorus in four (20%). In these. GC were sparse and the antral and pyloric GEC (score; p<0.01). The GC-ACB correlated much better with NL-ACB than did PC-ACB. These findings suggest that current techniques of HSV often do not provide reliable PC derervation, particularly in patients with ‘acid antrum’. These patients may be identified by preoperative histological examination of antral biopsies or peroperative Grassi test.

Effect of indomethacin on human gastro-duodenal 'mucus-bicarbonate' barrier

C J SHORROCK AND W D W REES (Hope Hospital, Salford) We have studied the effect of indomethacin on the 'protective' mucus-bicarbonate barrier overlying gastroduodenal mucosa in man. The pH gradient across fundic, antral and duodenal mucus gel was measured by a pH microelectrode inserted down an Olympus Q10 gastroscop. Mucosal integrity was graded endoscopically from 0 (normal) to 4 (severe damage) according to Lanza. In six healthy subjects (aged 22 to 35 years) with normal mucosa a pH gradient was measurable in fundus (maximum intramuraus pH=6.4±0.16), antrum (5.7±0.25) and proximal duodenum (6.6±0.1). Twenty four hours after starting indomethacin (50 mg tds) all subjects had mucosal damage (score: gastric=2.0±0.36; duodenum 0.66±0.33). At seven days of administration, damage persisted (gastric=1.8±0.56; duodenal 0.66±0.66) and two subjects developed discrete ulceration (one gastric and one duodanal). In the three subjects studied at 28 days of administration, all mucosal damage had resolved. Intramuraus pH remained unaltered at 24 hours and day seven, with only fundic mucus pH being slightly increased at day 28 (6.9±0.07, p<0.05, n=3). Antral luminal pH was significantly raised at 24 hours (3.35±0.59 compared with 1.81±0.15, p<0.02, n=6) returning to normal by day 28.

Indomethacin damages mucosa without altering intramuscular pH and there is evidence of mucosal adaptation with continued administration.

Acidification of the perfused human stomach during muscarinic-M1-receptor blockade stimulates gastric prostaglandin (PG) E2 output

A MERTZ-NIELSEN, I K MUNCK, K BUKHAVE, AND J RASK-MADSSEN (Departments of Medical Gastroenterology, Bispebjerg and Herlev Hospitals, University of Denmark) Pirenzepine dose-dependently increases duodenal HCO3 secretion, in addition to inhibiting gastric H+ secretion. Furthermore, duodenal acidification stimulates HCO3, and PGE2 output. To study the influence of gastric luminal acidification on muscarinic regulation of gastric PG release 'steady state' perfusions of the stomach were carried out in eight healthy volunteers during 'shamfeeding' before and after oral administration of pirenzepine (50 mg bid; four days). Luminal acidification (30 mM HCl) slightly decreased gastric peak acid output (PAO) (1.8±0.5 v control 2.6±0.3 mmol/15 min; mean±SEM; p<0.05), but caused no change in luminal PGE2 release (10.5±3.1 v control 8.2±1.5 ng/15 min). Pirenzepine reduced PAO (0.7±0.2; p<0.05) and a small rise in PGE2 output (13.9±5.2; p<0.05) was observed. Luminal acidification further decreased PAO (0.7±0.3; p<0.05) and markedly increased PGE2 release (21.9±6.6; p<0.05). This response was abolished (H+: 1±2±0.4; PGE2: 2.9±0.8; p<0.05) by indomethacin (100 mg iv). In conclusion, gastric mucosal PGE2 output was significantly increased by luminal acidification during muscarinic (M1) receptor blockade. The underlying mechanism may be important for the understanding of 'cytoprotection' and could explain why pirenzepine heals ulcers better than predicted from its acid inhibitory effect.

Polysaturated fatty acid ingestion and peptic ulcer – evidence for a direct relationship

H W GRANT, R W KELLY, K R PALMER, AND J MISIEWICZ (Gastrointestinal Unit, Western General Hospital and MRC Department of
Reproductive Biology, Edinburgh) The incidence and virulence of peptic ulcer disease has fallen in the Western hemisphere, as consumption of polyunsaturated fatty acids has increased. We have examined the effects of dietary polyunsaturated fat on gastric secretion, prostaglandin output and serum gastrin concentration. Nine healthy volunteers took 1.5 g or 3 g of linoleic acid (LA) for 14–21 days. Linoleic acid did not affect gastroduodenoscopic appearances, gastroduodenal histology, routine haematology nor serum and urinary biochemistry. Four subjects developed mild diarrhoea. Mean basal gastric acid output was 8.3±1.5 (SEM) mmol/h before LA and 7.2±1.3 (SEM) mmol/h after LA (p>0.05). Mean pentagastrin stimulated gastric acid output decreased from 35.2±3.5 to 30.1±2.8 mmol/h (p<0.05). There was a corresponding increase in mean serum gastrin concentration from 19.2±3.7 to 30.89±3.8 pg/ml (p<0.01). The mean output of immunoreactive PGE in gastric juice increased from 498±110 (SEM) ng/h to 1230±475 ng/h (p<0.05). The mean output of the main metabolite of PGE—13,14-dihydro 15-keto PGE$_2$ in gastric juice increased from 192±19 (SEM) to 1335 (±708) ng/h after LA (p<0.01). These data suggest an explanation for the observed relationship between dietary polyunsaturated fatty acid intake and peptic ulcer disease; polyunsaturated fatty acid ingestion modifies gastric prostaglandin metabolism with secondary changes in acid secretion and gastrin output.

A prospective, controlled trial of the garren gastric bubble (GB) with or without 600 calorie diet (D) on weight loss and gastric emptying (GE)

N Gemayel, J Laine, H Cohen, N Arnstein, and M Bossalis (introduced by J Valenzuela) (USC School of Medicine, Los Angeles, CA, USA) Controversy exists regarding the efficacy and physiologic effects of the GB. Sixteen obese women (age 30–58, BMI 32–52 kg/m$^2$) have been randomised into one of four groups (1) No GB, No D (n=4); (2) GB, No D (n=4); (3) No GB, D (n=3); (4) GB, D (n=5) and have completed a three month treatment period. All patients had endoscopy with real or sham GB insertion. Three month weight loss (kg): (1) −0.9±1.3, (2) −0.9±1.3, (3) −5.9±3.1, (4) −11.3±1.3; p<0.05 for variation among the mean weight losses and for 1 v 2 and 2 v 4. Liquid GE was significantly more rapid two weeks after GB insertion as compared to pre-GB: t$_1$: 11±2 v 19±3 min; time to duodenal visualisation: 3±1 v 7±1 min; % residual after 30 min: 17±2 v 32±5%. A significant correlation was seen between weight loss and the t$_2$ for liquids after GB insertion (r=0.82, p=0.007). Although an erratic solid GE curve developed after GB insertion, quantitative parameters of solid GE were not significantly different.

Interval results of this ongoing trial suggest (1) dietary instruction is the key factor in this weight loss program, (2) GB without dietary therapy is ineffective, and (3) liquid GE is significantly hastened after GB insertion.