The British Society of Gastroenterology

The 1989 Annual General Meeting of the British Society of Gastroenterology was held at Trinity College, Dublin, on 27 to 29 September, 1989 under the presidency of Dr J H Baron. Below are printed the texts of the 97 oral and 220 poster presentations selected by the Programme Committee of the Society from the 580 abstracts that were submitted to them.

GASTRODUODENAL I

High and low dose aspirin: equal gastric damage but impaired haemostasis at high dose

C J Hawkey, H K Sharma, N K Bhaskar, S M Didcot, A B Hawthorne, and I K Daneshmend (Dept of Therapeutics, University Hospital, Nottingham) The role of aspirin in upper gastrointestinal bleeding may reflect either ulcerogenicity (from inhibition of gastric prostaglandin (PG) synthesis) or bleeding provoked from existing lesions (because of impaired haemostasis, secondary to inhibition of platelet thromboxane)). We developed methods to differentiate these possibilities and compared high and low doses of aspirin.

Three groups of volunteers took aspirin ~ 300 mg (n = 12), 1.8 g (n = 10), or 2.4 g (n = 6) – for five days. Mucosal injury was measured endoscopically and spontaneous bleeding into washings was determined by orthotoluidine reaction. Platelet thromboxane production and ex vivo mucosal PGE2 synthesis (vortex mixing) were measured by radioimmunoassay. The gastric bleeding rate induced by biopsy was used as an index of haemostasis.

High dose aspirin inhibited gastric PGE2 synthesis by about 100% (median, interquartile range 82–100%, p < 0.01), causing endoscopic injury (Lanza grade 3 (1.5–3), p < 0.01, a 70 (3.1–57) fold increase in spontaneous bleeding (p < 0.01), and a 5.6 (3.4–12.2) fold increase in the gastric bleeding rate induced by biopsy (p < 0.01). Aspirin 300 mg/day caused less inhibition of gastric PGE2 (58% (30–100%) p < 0.01) but similar injury (Lanza grade 2.5 (2–4) p < 0.05) was seen at endoscopy. Both high and low dose aspirin inhibited platelet thromboxane by >90%.

Aspirin 300 mg is as gastrotoxic as higher doses and may be equally ulcerogenic. Higher doses provoke bleeding by impairing haemostasis and may differentially induce haematemia and melena. This impaired haemostasis, however, may be platelet independent.

Adaptation to indomethacin – induced gastric mucosal damage: histological and morphological correlates

C J Shorrock, R Prescott, and W D W Rees (Depts of Gastroenterology and Histopathology, Hope Hospital, Salford) Fourteen healthy volunteers underwent gastroscopy before and at one, seven, and 28 days after treatment with indomethacin (50 mg tds). Mucosal integrity was scored (0 (normal) to 4 (severe damage). Biopsy specimens were taken from normal looking mucosa. Specimens were examined histologically for Campylobacter pylori and scored for inflammation and regeneration using the scale 0 (not present) to 4 (severe changes).

All 14 subjects had macroscopic mucosal damage at day one (scores: 2.0 (0.2)). By seven days this damage had decreased in most patients, although two developed discrete ulcers (scores: 0.93 (0.32)). By 28 days adaptation was complete with all macroscopic mucosal damage having resolved in 10. Biopsy specimens were taken from 10 of the volunteers and in only three of these was the mucosa normal histologically before treatment with indomethacin. In the remaining seven, columnar lined oesophagus was seen in four. Histological appearances during indomethacin treatment were not significantly different to those before treatment, although there was a trend to more abnormal changes over the 28 day period (inflammatory scores in the antrum: 1.3 (0–4) before treatment and 1.5 (0–4) at day one, 1.7 (0.5) at day seven, and 1.9 (0.6) at day 28; scores in main body: 0.8 (0.3) before treatment and 1.3 (0.5) at day one, 1.2 (0–4) at day seven, and 1.5 (0.5) at day 28; scores for regenerative changes showed a similar pattern).

In conclusion, indomethacin produces focal mucosal damage with little evidence of histological abnormality. Adaptation to damage occurs through unknown mechanisms.

Indomethacin inhibits the normal regenerative response after experimental gastric ulceration

S Levi, D Vesey, S Kaifam, and J H Hodges (Depts of Medicine and Histopathology, Royal Postgraduate Medical School, Hammersmith Hospital, London) Gastric ulcers heal by a brisk glandular regenerative response at the ulcer edge. Prostaglandins stimulate this gastric proliferation and also protect against ulceration. We examined the hypothesis that non-steroidal anti-inflammatory drugs lead to gastric ulceration by inhibiting reparative regeneration at the ulcer edge, and that this inhibition should be reversed by giving prostaglandin at the same time.

Adult male Wistar rats received 10 days' treatment with (a) subcutaneous indomethacin (2 mg/kg/day), (b) oral misprostol (300 μg/kg/day), (c) indomethacin and misprostol ((a) and (b)), and (d) control vehicles. Two separate ulcers were then induced on the anterior gastric wall using a cryoprobe. The ulcer area and regenerative activity (using the BRDU-antiBRDU method) at the ulcer edge was determined on days three and six, during which period the above treatments were continued.

Indomethacin treatment resulted in larger ulcers (10.1 (1.3) mm2) than in controls (4.9 (0.6) mm2) (mean (SEM), p < 0.05), and caused a four-fold reduction in the regenerative activity at the ulcer edge (peak BRDU labelling per gland falling from 25 (6) to 8 (3)). Misprostol coadministration partially restored regenerative activity (to 14 (2) cells per gland) and also inhibited the indomethacin induced increase in ulcer size.

Indomethacin exacerbates gastric ulcer by inhibiting the normal regenerative

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response at the ulcer edge: this inhibition is reversed by misoprostol.

Campylobacter pylori and duodenal ulcers: the gastrin connection

S LEVI, K BEARDSHALL, J SWIFT, W FOULKES, R PLAYFORD, P GROSSI, J SPENCER, AND J CALAM (Depts of Medicine and Surgery, Royal Postgraduate Medical School, Hammer smith Hospital, London) There is strong epidemiological evidence that Campylobacter pylori (CP) causes duodenal ulcer (DU) disease. We have speculated that this is because CP stimulates antral gastrin release. We present an extended study of this effect plus those of eradicating CP.

Fifty one patients with active DU were studied. The urcse test performed on antral biopsies showed that seven were negative for CP and 44 positive. The peak pentagastrin stimulated acid secretion was 45-18 (3-0) mmol/h in the CP positive group compared with 29-7 (4-0) mmol/h in the CP negative group (mean (SEM) p<0.05). Integrated meal stimulated plasma gastrin responses were 1564 (267) pmol/min/l in the CP positive and 965 (248) pmol/min/l in the CP negative patients (p<0.05).

Ten CP positive patients were treated with metronidazole (400 mg tid) for two weeks and colloidal bismuth subcitrate (120 mg qid) for four weeks. Nine of these patients were CP positive after treatment. Integrated meal stimulated gastrin responses fell from mean (SEM) 1184 (350) to 498 (117) pmol/min/l (p<0.005).

We conclude that antral CP increases antral gastrin release and gastric secretion in patients with DU disease. Eradication of CP diminishes postprandial gastrin. We speculate that the CP urease splits urea to produce ammonia, thus raising the pH below the antral mucus layer and interfering with the feedback, inhibition of acid on gastrin release.

Effect of eradication of Campylobacter pylori on serum gastrin and gastric acid in duodenal ulcer

K E M McCOLL, G M FULLARTON, A MEL NJUMI, I I BROWN, A M MACDONALD, AND T W HILDITCH (University Dept of Medicine, Western Infirmary, Glasgow) Ten patients with Campylobacter pylori (CP) related antral gastritis and a history of duodenal ulceration were studied before and one month after a four week course of tri-

potassium dicitrate bismuth (De-Nol), metronidazole, and amoxycillin. Eradication of the organism, as judged by repeat antral microscopy, CLO-test and 13C-urea breath test, was achieved in nine patients. In these nine the median basal serum gastrin concentration fell from 30 (range 13-48) ng/l to 22 (range 8-30) ng/l (p<0.02), and the integrated gastrin response to an OXO meal fell from 3650 (range 1800-6025) ng/l/min to 1800 (range 1200-3075) ng/l/min (p<0.01). In the one subject in whom CP was not eradicated, the basal gastrin value was 30 ng/l before and 58ng/l after treatment, and the integrated gastrin response was 5275 kg/min before and 5450 ng/l/min after therapy. Twenty four hour intragastric pH was similar before (median daytime pH=1-3, median night-time pH=1-5) and after (median daytime pH=1-4, median night-time pH=1-3) eradication of CP. In five of the nine patients, night-time acid output (23:00-09:00 h) was also studied and was similar before, median (range) 86 (28-114) mmol/1 h and after 76 (58-143) mmol/1 h clearance of CP. Eradication of CP lowers circulating gastrin concentrations but this is not accompanied by any early change in acid secretion.

Surgery for medically resistant duodenal ulceration

W J CRISP AND C W VENABLES (Dept of Surgery, The Medical School, University of Newcastle upon Tyne) In a prospective, randomised study, 52 patients with a duodenal ulcer resistant to healing with H2-antagonists at double the normal dose were entered into a trial of vagotomy and antrectomy (group 1, n=25) or vagotomy and antrectomy (group 2, n=27).

Patients were assessed at five years, or earlier if they had further symptoms. In group 1, 21 (84%) patients had been reviewed, nine (42-9%) of whom were asymptomatic, and 12 (57-1%) pain free. One patient probably had a recurrent ulcer, but died of multi-organ failure after a major burn. In group 2, 18 (66-6%) patients have been reviewed, eight are symptom free and nine (50%) pain free. Ulcer recurrence has been found at endoscopy in six of these patients. Two have healed on medical treatment (one on omeprazole, one on cimetidine) and four underwent antrectomy. Postoperative gastric secretion studies have been performed on 14 (77-7%) patients from group 2; an incomplete vagotomy was found in two of these, one of whom has developed recurrent ulceration.

There is a high ulcer recurrence rate after vagotomy. If surgery is indicated vagotomy and antrectomy is the procedure of choice.

GASTRODUODENAL II

One hundred recurrent ulcers after highly selective vagotomy for duodenal ulcer: mortality, complications, and response to treatment

J G MARTIN, J N PRIMROSE, A T R AXON, AND D JOHNSTON (University Dept of Surgery, Department of Gastroenterology, The General Infirmary, Leeds) Highly selective vagotomy (HSV) is the most ‘physiological’ operation for duodenal ulcers (DU) but the incidence of recurrent ulceration (RU) afterwards has been high in some, though not all, series. In the past, RU after partial gastrectomy or vagotomy and drainage for DU led to serious complications and considerable mortality: was this true of RU after HSV?

Between 1969 and 1989, 990 patients with DU were treated by HSV and 100 developed endoscopically proved RU – 75 DU and 25 new gastric ulcers. The presentation was with perforation in one, haemorrhage in 10, and pain in 89. There were no deaths either from RU or a second operation. The median time to presentation with RU was 38-5 months (upper quartile 70, lower quartile 13 months). Duodenal ulcer presented earlier than new gastric ulcer (39 and 61 months, respectively p<0.05).

Medical treatment proved successful in 70 patients: 18 required only one course of H2-RA, 27 need intermittent treatment, and 25, maintenance H2-RA. Thirty patients required a second operation, four as emergencies and 26 electively.

After treatment of RU, 80% of patients were regraded Visick 1+11, 11% were regraded III, and 9% Visick grade IV.

Recurrent ulceration after HSV is less dangerous than RU after partial gastrectomy and has a better prognosis. Hence the grading of patients with recurrent ulceration after HSV as permanent failures of treatment is not justified.

Non-ulcer dyspepsia: a hypomotility disorder?

B WALDRON, P T CULLEN, D HOPWOOD, D SUTTON, N KENNEDY, AND F C CAMPBELL (Depts of Surgery and Medical Physics, Ninewells Hospital and Medical School, Dundee)
Dundee) Non-ulcer dyspepsia (NUD) is a common gastroenterological diagnosis with obscure aetiology. In this prospective study, 40 symptomatic patients were diagnosed as NUD after exclusion of peptic ulcer, gall stones, and oesophageal reflux by endoscopy, ultrasound, and 24 hour pH monitoring. Gastric and small bowel function were investigated by measurement of six objective parameters in all patients: (1) gastric emptying (GE), (2) oral to caecal transit time (OCTT), (3) antral Campylobacter pylori (CP), (4) small bowel bacterial overgrowth (SBBO), (5) peak acid output (PAO), and (6) enterogastric bile reflux (EGBR). All tests were validated in 20 healthy controls and abnormalities were defined as more than 2 standard deviations outwith the mean.

### Results of investigations of gastric and small bowel function in 20 patients with non-ulcer dyspepsia

<table>
<thead>
<tr>
<th>GE OCTT CP (delay)</th>
<th>SBBO PAO EGBR (++)</th>
<th>Patients (n) (%)</th>
<th>+</th>
<th>1</th>
<th>6</th>
<th>8</th>
<th>2</th>
<th>1</th>
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Twenty-nine of 40 patients had hypomotility, with delayed GE or prolonged OCTT, or both. All cases of bacterial overgrowth were associated with hypomotility.

In conclusion, hypomotility is common in NUD, is often accompanied by bacterial overgrowth and may be implicated in aetiology.

### Disordered motility in duodenal ulcer disease

D D Kerrigan, L A Houghton, M R Johnson, N W Read, and A G Johnson (Dept of Surgery and Sub Dept of GI Physiology, Royal Hallamshire Hospital, Sheffield) Disordered gastroduodenal motility may promote duodenal ulceration (DU) by allowing prolonged acid contact with duodenum. Using a multilumen perfused catheter, we recorded pressure activity in the antrum, pylorus (Dent sleeve), and duodenum in 35 subjects – 10 with active DU, 10 with healed DU, and 15 healthy volunteers. Intraluminal pH in the antrum and duodenum (two sites) was also recorded, correct pH catheter position being continuously verified by transmucosal potential difference measurements across the pylorus. Fasting recordings were made for 75 minutes and continued for 224 (18) min after ingestion of a radiolabelled burger.

### Postprandial duodenal motility

<table>
<thead>
<tr>
<th>Control</th>
<th>Active DU</th>
<th>Healed DU</th>
<th>p value*</th>
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<tr>
<td>34 (4)</td>
<td>23 (3)</td>
<td>22 (3)</td>
<td>0.05</td>
</tr>
<tr>
<td>6 (1)</td>
<td>12 (1)</td>
<td>12 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>4 (1)</td>
<td>10 (1)</td>
<td>8 (1)</td>
<td>0.03</td>
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Because the results of our intraduodenal pH recordings have already been reported to the BSG, we will concentrate on the motility analysis. Both active and healed DU patients had abnormal duodenal motility when compared with healthy controls, particularly after ingestion of the test meal (Table). The DU patients also showed a reduction in coordinated events propagated through the antrum during fasting. (control 12 (2) h; active DU 6 (1) h; healed DU 7 (2) h, p<0.05), although only healed DU subjects continued to show impaired antral coordination after the meal. Emptying of the beefburger was delayed in healed but not in active DU (healed T30=197 min, control T30=143 min; p=0.03).

Our results indicate a primary disturbance in gastrointestinal motility in DU disease, which may have important clinical and treatment ramifications.

### Is measurement of the rate of gastric emptying a valid assessment of gastric motility?

G H Ferguson and J V Taylor (Manchester Royal Infirmary, Manchester) In the intact stomach the rate of radionuclide emptying and motility are related, but this may not be so after vagotomy and drainage. A new, non-invasive radionuclide method, composed image analysis, has been developed which allows simultaneous measurement of gastric emptying and antral peristalsis. After ingestion of a radiolabelled meal, frames are taken at 2-5 second intervals over 35 minutes. Frequency, velocity, and strength of contraction are determined by computation.

Sixteen normal subjects were compared with 24 patients who had undergone truncal vagotomy and drainage (TVD) and eight patients who had anterior serompyotomy with posterior truncal vagotomy (ASM). There were no significant differences in the rate of emptying between normal subjects and the ASM group. Emptying was significantly faster in the TVD patients. Regular peristalsis was identified on the compressed image analyses of all the normal subjects, the eight ASM patients, and 12 TVD patients, but was absent in 12 TVD patients. There was no difference in the rate of emptying between the TVD patients whether they had peristalsis or not.

### Role of the proximal and distal stomach in emptying of high and low nutrient liquids in man

I A Houghton, Y F Mangnall, and N W Read (Dept of Surgery and Sub-Dept of Gastrointestinal Physiology, Royal Hallamshire Hospital, Sheffield) The relation between gastric emptying and intragastric distribution of a low (LNL) and high nutrient liquid (HNL) (300ml radiolabelled beef consumed with (455 kcal) and without (12 kcal) 60 g margarine) was investigated by performing randomised, paired gamma camera studies in seven male volunteers (20–22 years).

The LNL emptied rapidly from the proximal and distal stomach after a short lag period (4–6 min), during which time 24–50% of the liquid passed into the distal stomach. Addition of margarine increased the lag period (32 min 7–60 min; median: range: p<0.01) and decreased the slope of emptying [T50% period. 88 min (49–148 min) v 15 min (10–57 min); p<0.01]. During the lag period there was an initial rapid filling of the distal stomach, similar to that of the LNL, followed by a redistribution of distal stomach contents back into the proximal stomach [46% (19–61%); p<0.05]. At the onset of emptying the distal stomach refilled [25% (13–33%); p<0.05] and during this time the proximal stomach emptied twice as fast as the whole stomach (p<0.05). Thereafter, the distal stomach capacity remained constant while both the proximal and whole stomach emptied at similar rates.

This study shows that nutrient rich liquids are: (1) retained by the proximal stomach, and (2) redistributed from the antrum to the fundus before any apparent emptying occurs.

### Effect of partial gastrectomy and Roux diversion on gastric emptying in the rat

A D Houghton, P Lippins, N Aston, W J Owen, S Clarke, and R Mason (Depts of Surgery, Nuclear Medicine, and Radiological Sciences, Guy’s Hospital, London) We recently described a technique to...
measure liquid and solid gastric emptying in the rat on a sequential basis without animal sacrifice. We have used this to study emptying after partial gastrectomy and Roux diversion. Fifty male Wistar rats had liquid and solid emptying studies. Twenty-eight then had resection of two thirds of the glandular stomach, 18 with Polya reconstruction and 10 with Roux-en-Y diversion using a 10 cm Roux limb. There were 22 controls, 12 unoperated and 10 with a simple gastrotomy. Emptying was studied weekly for four weeks, then monthly for two months.

Emptying was unchanged in the unoperated controls. Gastrostomy alone had little effect on liquids but solid emptying was delayed until two months (p<0.05). Polya gastrectomy caused a greater initial retention of solids and liquids (p<0.05), but by four weeks emptying was faster than preoperatively (p<0.05). The addition of a Roux limb caused gastric retention of solids (p<0.05) and liquids (p<0.01) for three months.

This study shows that even minor surgery delays emptying. Gastric resection causes greater delay, which is prolonged by a Roux limb. This supports the theory in man that the addition of a Roux limb causes delayed gastric emptying.

Evidence for impairment of mucosal defence in reflux oesophagitis

P M GOGGIN, J MARRERO, J S DE CAESTECKER, C C W YU, C M CORBISHLEY, AND I C NORTHEILD (Dept of Medicine, St George's Hospital Medical School, London) An association exists between increased acid gastro-oesophageal reflux and distal oesophagitis. Some patients with oesophagitis, however, have very little acid reflux while others without oesophagitis have a considerable amount. Our aim was to test the hypothesis that impairment of oesophageal mucosal defence is also associated with reflux oesophagitis. We have assessed the ability of the oesophageal mucosa to repel aqueous solutions including acid – that is, hydrophobicity, by measuring the contact angle formed by a saline drop on the mucosal surface, using a goniometer.

We studied biopsy specimens of oesophageal mucosa obtained at endoscopy from patients with heartburn or dyspeptic symptoms (n=62). Specimens were from sites where there was no macroscopic evidence of oesophagitis (graded by the Savary-Miller classification). The contact angle (mean (SEM)) of the 30 patients with oesophagitis was found to be lower than that of the 32 without oesophagitis (38:0 (1:0) v 46:6 (0:7), p<0.0001). There was no correlation between severity of oesophagitis and the contact angle (Spearman R = -0.04).

We conclude that there is an abnormality in oesophageal mucosal hydrophobicity in oesophagitis and that this may represent a defect in mucosal defence.

Acid perfusion is a good screening test for symptomatic oesophageal reflux

P J HOWARD, L MAHER, A PRYDE, AND R C HEADING (Dept of Medicine, Royal Infirmary, Edinburgh) The role of the acid perfusion test (APT) in the diagnosis of symptomatic reflux has been questioned by the advent of ambulatory pH monitoring. We compared the APT with pH monitoring in 47 consecutive patients. Symptomatic reflux was diagnosed if 50% or more episodes of pain were associated with reflux events (fall of pH below 4) during ambulatory pH monitoring. Abnormal acid exposure time (AET) was taken as >7% of total recording time.

Eleven of the 32 patients who reported symptoms had symptomatic reflux (APT positive). 50% of the 23 patients without symptomatic reflux were APT positive (all five had normal AET). Fifteen patients were asymptomatic during the pH study (five APT positive, 10 APT negative). Acid exposure time was abnormal in seven of the patients with a positive APT and in nine of 26 with a negative APT. The sensitivity of APT was 100%, specificity 76%, positive predictive value 69%, and the negative predictive value 100% for the diagnosis of symptomatic reflux by our criteria.

(1) The APT has a very high sensitivity for detecting symptomatic reflux. (2) A negative APT makes symptomatic reflux improbable. (3) Symptomatic reflux or a positive APT, or both, can be found in patients with a normal AET. (4) A minority of patients with a positive APT do not have gastro-oesophageal disease.

Influence of treatment on oesophageal motility in gastro-oesophageal reflux disease

A P BARLOW, I R JENKINSON, C S BALL, I L NORRIS, AND A WATSON (Dept of Medicine, Royal Lancaster Infirmary, Ashton Road, Lancaster) Patients with gastro-oesophageal reflux disease often have abnormal oesophageal motility which may result in ineffective clearance of refluxed gastric juice. It is unclear whether this is a primary aetiological factor or a reversible consequence of pathological oesophageal acid exposure.

Forty-six patients with reflux oesophagitis underwent oesophageal manometry before and after a trial of ranitidine for up to six months. Eleven patients who subsequently had antireflux surgery were studied again three months later.

Patients with grade III oesophagitis had lower amplitude contractions in the distal two thirds of the oesophagus than those
with grade I oesophagitis (32 v 22, 50 v 26, 45 v 25, 55 v 22 mmHg, p<0.05). In 20 patients distal contraction amplitudes were less than the 10th centile of those recorded in 30 asymptomatic volunteers. Although oesophagitis healed in 16 patients and improved in eight after drug treatment, with healing in a further 10 patients after surgery, motility showed no significant improvement. Seven patients continued to have ineffective motility despite healing of oesophagitis.

The prevalence of ineffective oesophageal motility is increased in those with severe mucosal damage. These abnormalities are irreversible in most patients despite healing of the oesophagitis. Treatment is only likely to be of lasting benefit if it corrects one of the other aetiological factors.

Oesophageal investigation in non-cardiac chest pain – initial experience of a new clinical service

A VARGHESE and B J COLLINS (Dept of Medicine, The Queen’s University of Belfast) Recent research has shown that the oesophagus is often a cause of ‘non-cardiac’ chest pain. We report our findings in patients with chest pain referred to an oesophageal laboratory during its first year as a routine clinical service. Twenty two patients were referred by local cardiologists; 18 had typical anginal pain and four had non-specific chest pain. All had undergone recent coronary angiography (n=18), exercise testing, or electrocardiogram, or both, and were judged not to have cardiac chest pain, although two had previously suffered myocardial infarctions and three had undergone coronary artery bypass surgery. Baseline manometry was abnormal in eight of 22 patients. Edrophonium (80 µg/kg iv) reproduced chest pain in one of 21 patients (baseline manometry also abnormal). Twenty hour pH monitoring was abnormal in four of 13 patients but nine had usual chest pain during the study. Two had perfect correlation of pain with acid reflux, seven had pain coinciding with reflux on <50% of occasions. Three of five patients with previous infarction or coronary artery bypass surgery had a possible oesophageal origin of chest pain.

Oesophageal abnormalities are frequently encountered in the typically heterogeneous patients with ‘non-cardiac’ chest pain seen in routine practice. Edrophonium provocation is of no diagnostic value in this patient group.

Eventual diagnoses and outcome in patients discharged from coronary care with undiagnosed chest pain

A PANJU, E K DUKU, E FALLON, B GUHA, R H HUNT, H KENNEDY-SYMonds, D L SACKETT, D SLAVIK, S SOMERS, G W STEVENSON, D S WALTER, and W WATERFALL (Chedoke Division, McMaster University, Chedoke-McMaster Hospitals, Hamilton, Ontario, Canada) One hundred consecutive patients admitted to a coronary care unit with chest pain and discharged without a diagnosis of myocardial infarction, unstable angina, or other definitive cause for their pain were subsequently investigated. All underwent the following: medical history and physical examination, thallium scan, exercise testing, oesophageal studies, endoscopy and biopsy, 24 hour pH monitoring, acid perfusion, manometry with endophonium challenge, and cineluoroscopic barium meal; and were followed up (for mortality, morbidity symptoms, readmission for chest pain and social function).

Thallium scans were positive in 17% of patients, and 2% went on to have a cardiac arrest. Three per cent died, but none from a cardiac cause. At least one of the oesophageal studies (pH, endoscopy, motility, or barium cineluroscopy) was positive in 98% and all four tests were positive in 62% of patients. At six months, 67% were still having chest pain, but only 14% had been readmitted to hospital.

In this study, most patients with undiagnosed chest pain had real disease in the form of benign oesophageal disorders.

BASIC SCIENCE

Gastric secretion of pancreatic secretory trypsin inhibitor and its stimulation by misoprostol: a newly recognised protective mechanism

R J PLAYFORD, T FREEMAN, R A DAVIES, AND J CALAM (Dept of Medicine, Royal Post-graduate Medical School, Hammersmith Hospital, London) We have identified pancreatic secretory trypsin (PSTI) in gastric foveolar cells and investigated its potential cytoprotective role against refluxed duodenal enzymes. We measured basal gastric PSTI secretion and the effects of the prostaglandin E2 analogue misoprostol, which causes foveolar cell secretion, on its output. Test solutions, containing PEG 4000 to mark recovery, were sequentially perfused through the stomach of seven healthy volunteers at 5 ml/min for 40 minutes each. These were: 0-14 M saline, 0-17 M bicarbonate, bicarbonate with 400 µg misoprostol, then bicarbonate again. Aspirates contaminated with bilirubin or trypsin were discarded. A specific anti-human PSTI antibody T4 was used for radioimmunoassay.

When acid-peptic activity was abolished with bicarbonate, plateau rates of gastric secretion rose to mean (SEM), 16-4 (4) µg/h compared with a value of only 5 (1) µg/h with saline (p<0.0001). On adding misoprostol a further rise to 44 (10) µg/h occurred (p<0.005 v bicarbonate). These high values were maintained for at least 40 minutes after stopping misoprostol. Peak PSTI output was achieved after 200 µg of drug was given. equivalent to a single tablet of misoprostol.

Pancreatic secretory trypsin inhibitor is secreted into the stomach and its secretion is stimulated by misoprostol. Gastric secretion of PSTI may provide a ‘new’ protective mechanism against refluxed enzymes.

Ileal infusion of short chain fatty acids accelerates stomach to caecum transit time in the rat

A RICHARDSON, A T DELBRIDGE, N J BROWN, R D E RUMSEY, N W READ (Sub-dept of Gastrointestinal Physiology and Nutrition, University of Sheffield) We have previously shown that infusion of triglycerides and long chain fatty acids into the ileum of man and rats delays small bowel transit time. In our current experiments we investigated the effect of the ileal infusion of 20 mM, 50 mM, and 100 mM acetic acid; and 100 mM butyric, hexanoic, and caprylic acids on the stomach to caecum transit time of a baked bean meal in rats. After an 18 hour fast either a control or a short chain fatty acid (SCFA) solution (pH 6.5) was infused at a rate of 0.3 ml/h into the rat’s ileum for 30 minutes. A test meal was then given by gavage and the infusion was continued for a further 150 minutes. The arrival of the meal in the colon was signalled by a rise in exhaled hydrogen concentration. Acetic acid (20 mM, 50 mM, 100 mM), butyric acid (100 mM) and caprylic acid (100 mM) produced an appreciable acceleration of transit which was inversely proportional to the SCFA chain length. In a separate experiment infusion of 100 mM acetic acid, the most potent SCFA, into an isolated ileal Thiry-Vella loop failed to accelerate transit of the test meal. Our results suggest that SCFAs accelerate transit by a local enteric reflex.
Effect of L-365,260, a potent gastrin receptor antagonist on the in vitro growth of human and animal gastro-intestinal tumour cells

S. A. Watson, L. G. Durrant, and D. I. Morris (Cancer Research Campaign Laboratories, University of Nottingham, and Dept of Surgery, University Hospital, Nottingham) The gastrin receptor antagonist L-365,260 was assessed for its ability to compete with human gastrin-17 (G17) for binding to gastrin receptors on the rat pancreatic cell line, AR42J. In a competition assay with \( \frac{1}{125} \) I G17 (5 \times 10^{-10} M), the IC50 was 6 \times 10^{-10} M for G17 and 5 \times 10^{-10} M for L-365,260. Thus L-365,260 is 7-5 times less potent than G17 for binding to gastrin receptors on AR42J. Human gastrin-17 is mitogenic for AR42J cells as assessed by \([{35}S]\)-selenomethionine incorporation. L-365,260 (2-5 \times 10^{-10} and 2-5 \times 10^{-11} M) reduced G17 stimulated mitogenesis in three of four experiments (5 \times 10^{-10} M G17 inducing label uptake of 150 to 200% of control was reduced to 140 to 110% control). The effect of L-365,260 (2-5 \times 10^{-10}, 2-5 \times 10^{-11} M) was examined on the basal growth and G17-stimulated mitogenesis of freshly resected human gastrointestinal primary tumour cells. In 24 colorectal tumours six (25%) had significantly reduced basal growth as did two of two liver metastases and two of seven (29%) gastric tumours. In the same group of tumours seven of 18 (39%) colorectal, one of one liver metastasis and three of five (60%) gastric had significantly reduced responses to G17 in the presence of L-365,260.

L-365,260 is a potent gastrin receptor antagonist and could potentially be a valuable agent in the treatment of gut tumours in man.

Isolation and characterisation of intra-epithelial lymphocytes subsets in the normal colon

P. Hoang, M. Senu, J. R. Lowes, and D. P. Jewell (Gastroenterology Unit, Radcliffe Infirmary, Oxford) The characterisation of colonic intra-epithelial lymphocytes (IEL) using isolated cell populations has not been reported. The aim of this study was to isolate IEL from resected specimens of 'normal' colon and to characterise their phenotype. Intra-epithelial lymphocytes were obtained using a mechanical method from colonic resection specimens from eight patients – five with colonic adenocarcinoma and three with diverticular disease. The intestinal samples were taken at least 5 cm from any macroscopic lesions and were histologically normal. The IEL phenotype was determined using 12 pairs of monoclonal antibodies labelled with fluorescent isothiocyanate and phycoerythrin using multi-parameter flow cytometry.

Some 78-5 (20-1)% of IEL were CD3, 9-1 (4-3)% CD4, and 64-3 (19-9)% CD8. The mean ratio CD4/CD8 was 0.14. The contamination by B cells was less than 5%. The CD8 were mainly CD8+ + Leu8– (63-5 (18-9)). Most CD4+ cells were CD4+ Leu8− cells (helper-inducer T) and CD4+ CD45R− cells (8-7 (3-6)% of total lymphocytes). Although 15 (13-3)% of the cells expressed HLA-DR, only 1-9 (1-6)% expressed IL-2R. Few NC cells were detected using Leu7 monoclonal antibodies (Leu7+ , CD8− + 2-82 (2-2)% but 19-2 (13-45) of cells were CD3− , Leu11+ 19− (non-MHC-restricted NK cells) and 19-5 (9%) were CD3+ , Leu11+ 19+ (non MHC-restricted cytotoxic CD3+ T lymphocytes).

Using two colour immunofluorescence and flow cytometry, the IEL subsets are described in ‘normal’ colon mucosa.

Expression of cytokeratins by colorectal polyps

V. R. Sams, S. Shridhar, R. Davidson, and P. R. Boulds (Depts of Histopathology and Surgery, University College, London) A murine monoclonal antibody, CAM5.2, raised against a colon cancer cell line, recognises a low molecular weight cytokeratin present in colorectal carcinomas. We applied CAM5.2 to adenomatous polyps to determine whether detection of this antigen yielded further prognostic information. Sections of formalin fixed paraffin embedded colorectal polyps from 60 consecutive patients (27 men and 33 women) with a median age of 72 years (range 23-95) who had undergone colonscopic polypectomy were examined. A total of 63 polyps were stained with haematoxylin and cosin and immunohistochemically using the avidin-biotin technique: CAM5.2 antigen expression was graded 1-4 by the method of Ellis. No cytokeratin expression was found in three polyps, eight were graded 1, three graded 2, 12 graded 3, and 37 graded 4. Thirty four of the 63 polyps were rectal, 21 were in the sigmoid or left colon, and eight in the proximal colon. The CAM5.2 expression was less in the proximal than in the distal colon – five of eight proximal, two of 21 left colon or sigmoid, and seven of 34 rectal polyps having less than 50% cell stain (proximal v left colon/sigmoid, p<0.02). Of the 43 polyps measured before fixation, polyps greater than 0.5 cm diameter more commonly showed a greater than 50% cell stain than polyps of 0-5 cm or less (25 of 27 v 10 of 16, p<0.05). The antigen expression of the polyps did not vary significantly with histological type.

We conclude that cytokeratin recognised by CAM5.2 is expressed by most colonic polyps and with a greater staining intensity in polyps with high malignant potential identified by conventional histology. This further supports the malignant potential of polyps.

Antibody neutralisation of epidermal growth factor factor does not influence peptic ulceration

R. H. Gompertz, A. Garner, S. Michalowski, J. W. K. Barber, and R. C. N. Williamson (Department of Surgery and MRC Cyclotron Unit, Hammersmith Hospital, London and Biochemistry Department, ICi Pharmaceuticals, Macclesfield) Epidermal growth factor (EGF) both stimulates epithelial proliferation and inhibits gastric acid secretion. Since these effects reduce aggressive factors and promote defensive factors, EGF might have a role in maintaining gastroduodenal integrity. Reduction of luminal EGF by sialoadenectomy increases susceptibility to peptic ulceration and prolongs the healing phase.

In the present study we have determined the effect of removing systemic EGF by treatment with a neutralising antiserum. Activity was confirmed by the ability of the antiserum to prevent the inhibitory action of exogenous EGF on gastric acid secretion. Fifty six female CFLP mice weighing 25-40 g were randomly allocated to one of four groups. On day 0 animals underwent either lower mediastinal irradiation, which induces chronic duodenal ulcer in 10-45% of animals, or sham irradiation. On day one the two groups were split to receive 0-1 ml of either saline or anti EGF antiserum iv on days one and three. The incidence of duodenal ulcer was determined on day eight. No ulcers were seen in either the control or anti-EGF treated groups undergoing sham irradiation. Two of 14 mice (14%) irradiated and treated with anti-EGF bore typical ulcers. This is within the normal range and does not indicate an increase.

Removal of circulating EGF by a high affinity neutralising antiserum with a long half life does not cause spontaneous ulceration or increase ulcer yield in an established ulcer model over an eight day period.

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A1447
TAGH-induced hepatocyte DNA synthesis is associated with epidermal growth factor (EGF) receptor phosphorylation and down-regulation

D VESEY, A C SELDEN, AND H J F HODGSON (Dept of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) Readily available hepatotrophic factors would constitute valuable treatment tools. DNA synthesis can be induced in intact rat liver in vivo by Tri-iodothyronine (10⁻³ M), 8.5% amino acid solution, glucagon (10⁻³ M) and heparin (10 U/ml) (TAGH). We investigated the mechanism of TAGH-induced hepatic DNA synthesis, with particular reference to known pathways of hepatocyte proliferation including EGF. An intravenous TAGH solution infused over three hours induced a mean 10⁻⁹-fold increase (n=8) in "H-thymidine incorporation into liver in 24 hours. Membrane studies after TAGH showed a 20% reduction in "I-EGF binding, with Scatchard analysis indicating no change in affinity, paralleling the EGF receptor down regulation induced by partial heptectomy. The possibility that TAGH released EGF in vivo was considered, but TAGH also enhanced DNA synthesis in rat hepatocytes in vitro. Furthermore, we showed that TAGH induced tyrosine phosphorylation of the 170 kD EGF receptor on liver cell membranes in vitro, as does EGF. TAGH-induced hepatocyte proliferation is therefore associated with down regulation and phosphorylation of EGF receptors, and probably acts via recruitment of this pathway of hepatocyte stimulation.

Effects of osmotic stresses on intracellular pH in rat hepatocytes: implications for cell volume regulation

D GLEESON, J G CORASANTI, AND J L BOYER (Dept of Medicine, Liver Centre, Yale University School of Medicine, Newhaven, Connecticut, USA) In several cells, volume regulation in response to hypotonic and hypertonic stresses is partly mediated by parallel Na⁺/H⁺ and Cl⁻/HCO₃⁻ exchange. We therefore assessed the effects of osmotic stresses on rat hepatocyte intracellular pH (pHi), using a continuously perfused sub-confluent monolayer cell culture system and the pHi sensitive dye BCECF.

Hypotonic stress (HYPO) in the absence of HCO₃⁻ caused the pHi to fall from mean (SD) 6.98 (0.11) to 6.85 (0.08). Returning cells to isotonic medium (relative hypertonic stress, HYPER) caused the pHi to rise to 7.15 (0.15). Both the fall and the subsequent rise in pHi were abolished by Na⁺ removal or by 1 mM amiloride, suggesting mediation by Na⁺/H⁺ exchange. HYPO and HYPER caused similar but smaller pHi changes in the presence of HCO₃⁻ (because of greater intracellular buffering capacity). These pHi changes in HCO₃⁻ were unaffected by acute Cl⁻ removal, evidence against mediation by Cl⁻/HCO₃⁻ exchange.

Hepatocyte Na⁺/H⁺ exchange is activated during HYPER and inhibited during HYPO, consistent with a role in hepatocyte volume regulation. A corresponding role for Cl⁻/HCO₃⁻ exchange cannot be shown.

Liver cell co-cultures show enhanced survival and protein synthesis

A J WOODMAN, J C CUNNINGHAM, AND H J F HODGSON (Dept of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) Primary hepatocyte cultures are valuable tools for investigating liver metabolism; but they are short lived and show a progressive decline in synthetic function. We have developed co-cultures of rat hepatocytes with Kupffer-cell-rich non-parenchymal cells. After collagenase perfusion, non-parenchymal cells were separated by Percoll density gradient and plastic adherence, and cultured for six days before adding fresh primary hepatocytes. Co-cultures were compared with hepatocytes on collagen coated plastic. Hepatocyte cell numbers were enhanced in co-cultures at all time points, with mean (SD), 1-5 (0-4) times as many cells (n=4, observations in triplicate) on day five and 2-83 (0-7) times on day seven. "H-Thymidine incorporation assessed biochemically and by autoradiography showed that this was the result of enhanced survival rather than proliferation. Co-cultures secreted twice as much newly synthesised protein (6-8 v 3-4% [³⁵S]-leucine incorporated over 24 hours) with similar changes in albumin secretion (850 ng/ml v 420 mg/ml over 24 hours in seven day cultures).

Co-cultures of hepatocytes with these non-parenchymal cells enhances synthetic capacity and cell survival without enhancing proliferation, permitting analysis of paracrine control of liver metabolism in an environment akin to circumstances in vivo.

Ability of sandostatin (SMG-201,995) to reduce the growth of gastrointestinal cancer cell lines and fresh ex vivo human cancer cells

S A WATSON, A L WATSON, I G DURRANI, AND D L MORRIS (Cancer Research Campaign Laboratories, Nottingham University and Dept of Surgery, University Hospital, Nottingham) The effect of sandostatin (SMS-201,995) on the basal and gastrin-stimulated growth of gastrointestinal cancer cells was examined by [³⁵S]-selenomethionine incorporation. SMS-201,995 (1000 to 10 ng/ml) reduced the response of LoVo (human colorectal cell line) to human gastrin-17 (G17 5×10⁻⁶ M) from 167% to 81% of the control value (p<0.001). The basal growth of ARJ2J (rat pancreatic) was reduced by SMS-201,995 to between 10 and 30% and the response to human G17 was reduced (typical experiments: 10⁻⁶ M G17, 174% down to 50% of control value). MKN45 (human gastric) has intracellular gastrin-like immunoreactivity. The basal growth of the cell line was modestly reduced by SMS-201,995 (80% of control, 1000–10 ng/ml). All three cell lines were positive for SMS receptors as measured with an iodinated derivative of SMS-201,995. SMS-201,995 (1000 ng/ml) reduced the basal growth of 8 of 21 (38%) primary human colorectal tumours, one of two gastric tumours and one of one liver metastasis. The growth response to G17 was assessed in the same group of tumours and four of 16 (25%) colorectal tumours. One of two gastric tumours, and none of one liver metastases had reduced responses to G17 in the presence of SMS-201,995 (1000 ng/ml). SMS-201,995 may have a role in the treatment of gut tumours.

Regulation of expression of the epidermal growth factor (EGF) receptor in gastrointestinal cancer cell lines

A HALL, D L MORRIS, S A WATSON, AND I G DURRANI (Cancer Research Campaign Laboratories, Nottingham University and Dept of Surgery, University Hospital, Nottingham) Expression of the EGF receptor on gastrointestinal tumours may be of prognostic importance and is a putative target for treatment. In order to establish models for screening these agents, recently established cell lines, four colorectal (C146, 168, 277, and 280) and two gastric (MKN45 and ST42), were studied. Three cell lines had modest levels of expression which when expressed as a percentage of binding to A431, a human epithelial cell line with high binding, were: C168, 8·1%; C280, 40%.

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5.9%; and ST42, 4.5%. Three cell lines had high levels of expression (MKN45, 14.8%; C146, 22%; and C277, 21-45% of A431). Southern blot analysis of MKN45, ST42, and C168 and 146 indicated that the different levels of receptors are not due to amplified copy number of the human EGF receptor gene. All the cell lines had functional EGF receptor as measured by EGF mobilised calcium flux. In mitogenicity studies both C146 and ST42 responded modestly (135+2% of control). Furthermore, a factor secreted by ST42 was found to inhibit binding of EGF to its receptor suggesting that an EGF-like factor may have autocrine stem.

Relationship of tissue and tumour fatty acids to dietary fat in experimental colorectal cancer

M SAKAGUCHI, C IMRAY, S ROWLEY, N KANE, A DAVIS, C JONES, P BAKER, M KIGHTLEY, J P NEOPOLEMOUS (University Dept of Surgery and Dudley Road Hospital, Birmingham)
The growth of 1 x 10^6 cells sc in 90 nude mice of two colorectal cancer cell lines was reduced by a diet high in n-3 fats (40%) (diet A) compared with a diet of saturated fat (82%) (diet B), and a standard diet of saturated fats (50%) and oleate (40%) (diet C). HT-29 tumour weight at four weeks (mean (SD)) on these diets was: A=0.26 (0.16) g, B=0.49 (0.25) g, C=0.46 (0.46) g, p<0.05; and the values for colo-320 were: A=0.28 (0.16), B=0.60 (0.34), C=0.41 (0.31), p<0.02.

On diet A, n-3 fatty acids were greatly increased in red cell membranes, adipose tissue, and tumour lipids; on diet B saturated fats and linoleate were increased in adipose tissue, and linoleate and arachidonate were increased in red cells and tumour (all p<0.001). The most striking effects were seen in the metabolically labile phospholipid fraction of tumours; on diet A there was decreased arachidonate and increased cicosapentaenoate, docosapentaenoate, and docosahexaenoate. The latter are inhibitors of arachidonate metabolism suggesting that this is the mechanism of tumour growth suppression by dietary n-3 fats.

Lectins modulate growth in HT29 colon cancer cells

S D RYDER, E G RHODES, J A SMITH, AND J M RHODES (University Dept of Medicine, Haematology, and Biochemistry, University of Liverpool and Walton Hospital, Liverpool) Malignant cells commonly exhibit altered lectin binding, but the functional importance of this is unclear. To determine whether lectins can modulate growth in cancer cells, HT29 cells were maintained in low growth for 40 hours in the presence of wheat germ agglutinin (WGA), concanavalin A (con A), arachis hypogea (PNA), or Ulex europaeus (UEA1) at eight concentrations from 1 to 100 μg/ml. Twenty five wells of 10^6 cells were used at each concentration with 45 control wells (no lectin). These were pulsed for 18 hours with [H]thymidine. PNA caused a 43 (0.8) fold stimulation (mean (SE)) of thymidine incorporation at concentrations above 6 μg/ml (p<0.01), WGA and con A caused stimulation at low concentrations, WGA 38 (1.2)% at 3 μg/ml, con A 48 (2.0)% at 6 μg/ml (p<0.01), but inhibition above 25 μg/ml. WGA 96 (0.1)% inhibition at 50 μg/ml, con A 77 (0.5)% inhibition at 50 μg/ml (p<0.01). UEA1 had no significant effect. Cell counts after four days incubation confirmed these effects on growth. Cell viability (trypsin blue) was 95% at inhibitory concentrations.

This study shows potentially important growth regulatory effects of lectins on colon cancer cells.

Production of epithelial cell growth factors by lamina propria mononuclear cells

J R LOWES, J D PRIDDLE, AND D P J-FELL (Gastroenterology Unit, Radcliffe Infirmary, Oxford) Epithelial cell growth factors from lamina propria mononuclear cells (LPMMC) were examined by an ELISA technique to quantitate the incorporation of bromodeoxyuridine (BrdU) into the colon epithelial cell line HT29. In each experiment a stimulation index (SI) was calculated. LPMMC isolated from colon wall biopsies from patients with ulcerative colitis (UC) (n=10), and controls (>5 cm from colon cancer) (n=10), were cultured for three days ±0.1 μg phytohemagglutinin (PHA) and supernatants were harvested. The SI of supernatants from UC patients (median 8.6 (1.0-27.1) did not differ from controls (median 9.35 (1.1-31.6). Activity of supernatants from PHA stimulated cells was significantly greater than from unstimulated cells (UC 37.0 (5.2-72.8)), control 33.5 (3.6-89.2) (p<0.05). Activity was destroyed by boiling and exposure to pH2, but not trypsin. Gel chromatography of concentrated supernatant identified active fractions in the range 30-48 kD. Fractions with MW<17 kD inhibited BrdU incorporation. Peak fractions were pooled and passed onto a chromatofocussing column. Two active fractions were identified with pK of 6.4 and 5.5.

In the same assay system, recombinant interferon-γ, and interleukins 2 and 3, had no effect on SI. Interleukin-1β inhibited and granulocyte-macrophage colony stimulating factor was a potent stimulus to BrdU incorporation in HT29 cells (20 U/ml GM-CSF SI=129 (29)). Cytokine, and in particular GM-CSF, production by activated LPMMC may be important in the control of epithelial cell growth.

Prostacyclin – evidence for a dual secretory mechanism in mammalian colon

K J MORIAI, N B HIGGS, A TONGE, M LEES, T D WARDLE, AND G WARHUSTR (Dept of Medicine, Hope Hospital, University of Manchester School of Medicine, Salford) Prostacyclin (PGI2) is an arachidonic acid metabolite synthesised throughout the gastrointestinal tract. We have examined the mechanism of action of PGI2 in mammalian colon. Segments of distal colon of male Sprague-Dawley rats were stripped of muscle layers and mounted in flux chambers. PGI2 (10^-10 M) caused a rapid rise in short circuit current (Isc) and transmucosal potential difference (PD). A rise in Isc and PD is generally associated with enhanced secretion. PGI2 has previously been shown to elicit secretion in rat colon by a Ca^2+/-calmodulin (CDR)-dependent neurogenic mechanism. We examined whether PGI2 also acts directly on human colonocytes by adding PGI2 to T84 colon carcinoma cells grown in flux chambers. PGI2 (10^-5 x 10^-7 M) evoked a dose-dependent rise in Isc and PD. Previous studies have shown that the addition of Ca^2+/-mediated agonists to T84 cells which had been pretreated with secretagogues acting via cyclic AMP, provokes a synergistic stimulation of Isc. We thus examined the influence of carbachol (10^-8 M) on the effect of PGI2 (5x10^-10 M). Carbachol caused a 220% stimulation in the response. Moreover, carbachol (10^-4 M) pretreatment inhibited the subsequent Isc response to PGI2 (10^-7 M) by 60%. PGI2 (5x10^-10 M) stimulated a two to three-fold rise in cellular cyclic AMP when incubated with T84 cells. PGI2 may thus provoke secretion in mammalian colon by two mechanisms – namely, an indirect Ca^2+/-
CDR-dependent neurohumoral reflex, and also directly or human colonocytes via activation of intracellular cyclic AMP.

Acute undernutrition enhances intestinal secretion induced by secretagogues acting via Ca++ and cyclic GMP but not cyclic AMP

A Young and R J Levin (Department of Biomedical Science, University of Sheffield, Western Bank, Sheffield) The role of acute undernutrition (AU) on diarrhoeal mechanisms was examined in rats fed 33% of their normal dietary intake per day for nine days. Fluid transport was measured in the jejunum and ileum of the rats using a gravimetric technique. The jeuna of fed control and AU rats had similar basal values of fluid absorption. The ilea of the AU rats, however, showed a small secretion compared with the absorptive tone in the controls (p<0.001). After stimulation with the muscarinic agonist bethanecol (60 µg/kg, ip), both the jejunum and ileum of the AU rats displayed greater fluid secretion than the controls (p<0.001) mainly because of increased Cl secretion. Stimulation by the prostaglandin PGE2 (10 µg/kg, ip) induced similar levels of secretion in jejunum and ileum of control and AU rats. Luminal application of Escherichia coli enterotoxin STa (500 ng/ml), however, caused greater secretion in the jejunum and ileum of AU rats (p<0.001). Acute undernutrition has specific effects on the secretory mechanisms activated intracellularly by Ca++ (bethanecol) and cGMP (E Coli STa) but not on those controlled by cAMP (PGE2).

Campylobacter pylori lacks immunoglobulin A1 protease

J Huang, C J Smyth, N P Kennedy, and P W N Keeling (Dept of Microbiology, Mayne Institute and Dept of Clinical Medicine, Trinity College, Dublin Medical School, St James's Hospital, Dublin) Immunoglobulin A (IgA) proteases are putative virulence factors produced by mucosal pathogens including several Gram negative bacterial species—for example, Neisseria meningitidis, Haemophilus influenzae and Bacteroides melaninogenicus. These enzymes are serine proteases. They cleave only IgA1 because the protease sensitive, proline rich sequence of its hinge region is lacking in IgA2.

Six strains of Campylobacter pylori were grown in serum broth and on lysed blood agar media. The harvested cells were incubated with pure human serum IgA1. Streplococcus pneumoniae, a well characterised producer of IgA1 protease, was used as a positive control for IgA1 cleavage. Incubation mixtures were separated by agarose immunoblotting and diffused against anti-human IgA. Whereas cleavage of IgA1 protease was readily shown by the S pneumoniae control, no cleavage products were observed with the C pylori strains, even after prolonged incubation with the IgA1 substrate. It is concluded that C pylori does not elaborate an IgA1 protease.

Restitution of rat gastric mucosa in vitro

J Li, D C Hanley, R C Mason, P H Rowe, and I McColl (Dept of Surgery, Guy's Hospital, United Medical and Dental School, London and Dept of Surgery, Eastbourne District General Hospital, Eastbourne) Restitution of gastric mucosa in vitro has been previously described in amphibia but not in the rat. This study aimed to investigate restitution of rat gastric mucosa in vitro. Using chambered mucosa exposed to 0.75 M NaCl for 10 minutes in a luminal chamber exhibited an immediate fall in potential difference (PDmv) from baseline values of mean (SEM) -27-63 (4.48) to -1.9 (0.8) (p<0.01) and resistance (R, ohm/cm²) from 87.5 (7.2) to 21.7 (8.9) (p<0.01). Acid secretion decreased from 2.77 (1.42) to 0.11 (0.23) mmol/cm²/h. Tissues removed (n=4) after NaCl exposure exhibited severe mucosal injury with surface ulceration. After 10 minutes of NaCl exposure and replacement with normal luminal solution, tissues (n=8) were allowed to recover for two hours. All tissues showed evidence of histological reconstitution of surface epithelium. PD recovered to 50% of control values 9.5 (5.0) (p<0.01) and R values were similar to controls 80.7 (24.7) (ns). Acid secretion recovered to 0.18 (0.28) mmol/cm²/h (p<0.05) and controls. Control tissues maintained in normal luminal solution (n=7) for two hours exhibited no histological damage. This study shows that gastric mucosal restitution occurs in the rat within two hours but recovery of parietal cell function is not complete.

Molecular basis for gastric mucosal hydrophobicity

P M Goggin and T C Northfield (Dept of Medicine, St George's Hospital Medical School, London) We have shown that the human stomach has a hydrophobic lining which may be important in mucosal defence, and that hydrophobicity is reduced in peptic ulcer disease and in Campylobacter pylori infection. In vitro studies have shown C pylori to possess phospholipase A2 activity which will convert the hydrophobic phosphatidylycholine (PC) into the more hydrophobic lysophosphatidylycholine (LPC). In studies on porcine gastric mucosa, we have shown mucosal hydrophobicity to be dependent upon the mucin layer. The aim of the present study was to determine whether there is a relation between hydrophobicity and the phospholipid composition of the mucous layer.

We studied mucin scraped from porcine stomachs (n=9) immediately after slaughter. Contact angles (CA) of saline drops were measured on mucin samples using a goniometer as an index of hydrophobicity. PC and LPC were measured on a Folch extract of mucus by HPLC. CA correlated with PC (r=0.47, p<0.05) and negatively with LPC (r=0.57, p<0.01). It correlated best with the ratio expressed as log PC:LPC (r=-0.82, p=0.006).

We conclude that mucosal hydrophobicity is related to the phospholipid composition of the mucous layer. This provides a molecular basis for gastric mucosal hydrophobicity and suggests a novel explanation for impairment of mucosal defence by C pylori.

Histological damage follows a decrease in prostaglandin E2 synthesis in a cysteamine model of duodenal ulceration

S Pugh and R J Levin (Dept of Surgery, Rayne Institute, University College, London) It has been suggested that changes in prostaglandin synthesis in duodenal ulcer are related to tissue damage and are not causally associated with the formation of the ulcer. No study has looked at prostaglandin synthesis during ulcerogenesis and related this chronologically to historical assessment of damage. We used a cysteamine model of duodenal ulceration in groups of 10 female wistar rats—a control group and groups at six, 18, and 24 hours after im injection of 30 mg cysteamine/100g body weight. Prostaglandin E2 synthesis in duodenal mucosa was estimated after the method of Whittle and Salmon (1982). Histological scoring for changes was suggested by Nishizaki and Ashizawa (1985) (possible range 5-20). There were four premature deaths. The histological scores were (n=10 except Gp 24 h): controls—8.4 (2.8), 6 h—10.2 (2.99), 18 h—14.6 (2.33), and 24 h—16.5 (3.4) (n=6). The 6 h group...
was not different to controls, but the 18 and 24 h groups showed increased damage compared with controls (p<0.001; Student's t test). Prostaglandin F₂α synthases were (pg PGE₂/mg) 153.8 (25.8), 84.3 (17.2), 56.4 (12.6), and 54.3 (19.6) (n=6) respectively. All three treatment groups synthesised less PGE₂ than the control (p<0.001; Student's t test). Regression analysis of histological features correlated negatively (p<0.001) in the treated groups. Decrease in prostaglandin synthesis can precede histological damage and in treatment groups this fall in synthesis of PGE₂ correlates with increasing histological damage.

Sulphasalazine promotes mononuclear cell prostaglandin production

N A PUNCHARD, D J BOWEEL, AND R P H THOMPSON (Gastrointestinal Laboratory, Rayne Institute, St Thomas' Hospital, London) Sulphasalazine has been reported to either inhibit or stimulate prostaglandin (PG) production in inflammatory bowel disease. These effects on PG metabolism may depend on the drug concentration, degree of cellular stimulation, and the PG measured. We therefore investigated the effects of either 0, 0.1, or 10⁻¹ to 10⁻³ mol/l sulphasalazine on non-stimulated or LPS (10 mg/ml) stimulated PG production, measured by radioimmunoassay, in 24 hour incubations of 1x10⁶ mononuclear cells/ml prepared from peripheral blood of four healthy volunteers.

Sulphasalazine enhanced LPS-stimulated production of all PGs slightly at 10⁻¹ mol/l, but more noticeably at 10⁻³ mol/l (324, 192–370% for PGE₂; 161, 158–259% for 6κF₁α; 143, 136–215% for PGE₂; 161, 158–259%, % of control value; median, range). At 10⁻¹ mol/l PGE₂ production was still stimulated, but stimulation of 6κF₁α and PGE₂ production was appreciably reduced with evidence of inhibition, which may be due to a toxic effect of sulphasalazine on the cells. Similar results were obtained in unstimulated incubations. The results may explain the variability of previous reports and suggest that the mechanism of the therapeutic action of sulphasalazine is through promotion of production of cytoprotective PGs.

Evidence of decreased electroneutral sodium absorption during cholela toxin induced secretion in human jejunum

J HUNTER, A V THILLAINAYAGAM, S CARNABY, M L CLARK, AND M J G FARTHING (Dept of Gastroenterology, St Bartholomew's Hospital, London) Cholela toxin has been shown to decrease electroneutral Na⁺/H⁺ exchange in mammalian small intestine in vitro. We therefore studied electroneutral sodium absorption in man in an experimental model of cholela. Highly purified cholela toxin (25 μg) was introduced into a 30 cm segment of proximal jejunum, isolated between two occluding balloons. Two hours later the balloons were deflated and the jejunum was perfused by the triple lumen technique. As bicarbonate stimulates electroneutral absorption in normal jejunum we perfused a saline bicarbonate solution (Na 140, K 4, HCO₃ 40, Cl 104 mmol/l) at 15 ml/min. At five hours, sodium absorption occurred in controls (429–1 (94–7) μmol/cm/h; n=6) and secretion in cholela toxin treated subjects (590.6 (191-9; n=8; p<0.01). Bicarbonate absorption (an indirect indicator of electroneutral sodium absorption in the jejunum) was decreased in cholela toxin treated individuals (3–6 (3–1) μmol/cm/h; n=8) compared with controls (244–5 (52–6; n=6; p<0.01).

While it is difficult in an in vivo system to study individual transport events our findings are consistent with the view that cholela toxin decreases the activity of the Na⁺/H⁺ antiport and thus supports previous studies in vitro. This process may be important in the production of diarrhoea in cholera.

Immunological involvement of Brunner's glands in coeliac disease

R B GALLAGHER, O SHEILS, AND D G WIEH (Depts of Immunology and Clinical Medicine, Trinity College Medical School, St James' Hospital, Dublin) The glands of Brunner play an important part in the defence of the mucosa via secretion of bicarbonate, mucus, and epithelial growth factor (EGF). We previously showed decreased EGF values in duodenal aspirates from coeliac patients. The present study suggests that the Brunner's glands are the targets of immunological reactivity in coeliac disease.

Immunoperoxidase staining was performed on frozen sections cut from duodenal biopsy specimens from patients with treated and untreated coeliac disease and normal and disease (duodenal ulcer and duodenitis) controls. The following monoclonal antibodies were used: 3B1, which detects a complement activation antigen: anti-HLA-DR, DQ, and DR to detect HLA class II antigen expression; and anti-CD3, CD4, and CD8 to assess T lymphocyte infiltration.

Complement activation within the duodenum was exquisitely restricted to the Brunner's glands and was detected in each of the untreated (n=5) and treated (n=5)
biopsy specimens examined, but in only three of 13 disease controls. HLA class II antigen expression occurred in six of nine coeliac patients (three of three untreated and three of six on gluten free diet), and in two of seven disease controls. Preliminary results on T lymphocyte infiltration showed appreciable increases in both CD4 and CD8 cells in coeliac biopsy specimens compared with normal controls. A similar infiltrate was also noted in one of six disease controls.

Brunner’s glands are mainly located in the proximal duodenum where, interestingly, the mucosal abnormality of coeliac disease is most noticeable. The findings of immunological activity within the glands may be of pathogenic importance.

Soluble interleukin-2-receptors in the serum of patients with coeliac disease: effects of treatment and gluten challenge

J E CRABTREE, R V HEATLEY, I D JUBY, P D HOWDLE, AND M S LOSOWSKY (Dept of Medicine, St James’s University Hospital, and Gastroenterology Unit, The General Infirmary, Leeds) T lymphocytes have been implicated in the pathogenesis of the coeliac lesion. Activated T cells secrete interleukin-2 (IL-2) and express cell surface receptors for this growth factor (IL-2R). To assess the extent of immune activation in patients with coeliac disease, we have measured by ELISA serum concentrations of a stable, soluble form of the interleukin-2 receptor (sIL-2R) which is released from activated lymphocytes.

The mean (SEM) serum sIL-2R value in untreated coeliac patients (1324 (233) U/ml; n=15) was significantly greater (p<0.001) than that of patients with treated coeliac disease (519 (60-3); n=24), age and sex matched control patients who had normal jejunal histology (249 (22-4) and nonsymptomatic controls (186 (25-9). Longitudinal studies in individual coeliac patients (n=10) showed that serum sIL-2R fell after beginning a gluten free diet. Gluten challenge (30 g/day for one week) of treated coeliac patients (n=16) resulted in a significant increase (p<0.05) in serum sIL-2R, which returned to prechallenge values within four weeks of restarting of a gluten free diet.

These data suggest that serum sIL-2R values in patients with coeliac disease reflect specific immunological activation in response to gluten ingestion and the results are supporting evidence for the role of T-lymphocytes in the pathogenesis of the coeliac lesion.

Reduced intestinal calmodulin activity in coeliac disease

J AMOAH, C WILLIAMS, AND R G LONG (Medical Research Centre, City Hospital, Nottingham) Calcium malabsorption is a complication of coeliac disease. Calmodulin is a major calcium binding protein that modulates some calcium dependent cellular processes and acts as a calcium buffer in intestinal epithelia.

The aim of this study was to measure intestinal calmodulin content in patients with and without coeliac disease (CD). Two methods that are commonly used to measure calmodulin are radioimmunoassay (RIA) and calmodulin stimulated phosphodiesterase activity (PDE). The PDE assay measures biologically active calmodulin whereas the RIA is based upon the recognition of antigenic determinants.

Calmodulin values were measured in extracts of duodenal biopsy specimens from 25 patients with histologically normal mucosa and from 11 patients with CD. Results are expressed as mean (SEM) μg calmodulin/mg protein. The RIA gave values of 1.79 (1.1-2) for normal and 1.93 (1.16) for CD mucosa (p<0.05). The corresponding values with the PDE assay were 1.98 (1.1-2) and 1.46 (1.2) (p<0.05).

The calmodulin antagonists, trifluoroperazine (TFP) and a N-(6-amino-5-chloro-1-naphthalene) sulphamide derivative (IDOD 8) were used in the PDE assay to investigate these differences. PDE activity was inhibited 64 (1-1)% and 91 (1-2)% (n=5) by 9 μM and 90 μM TFP respectively in normal mucosa and 64 (3-2)% and 88 (1-5)% (n=5) in CD. With 3 μM and 10 μM IDOD 8, PDE activity was inhibited 22 (5-3)% and 68 (3-7)% (n=5) in normal and by 20 (2-0)% and 74 (4-2)% (n=5) in CD respectively. There was no significant difference between the two groups at any of the concentrations.

These results suggest there is a reduction in biologically active calmodulin in patients with coeliac disease.

Raised fasting breath H₂ values in coeliac disease caused by fermentation of increased endogenous substrates

G R CORAZZA, A STROCHI, M SORGE, M C LATTANZI, E A TREGGIARI, R VALENTINI, AND G GASBARRINI (I Patologia Medica, Policlinico S Orsola, University of Bologna, Italy) Recent studies have shown that in Ireland the prevalence of splenic hypofunction (SH) is 76% in patients with untreated CD and 20% in their first degree relatives. Using the same method to evaluate splenic function, based on the pitted cell (PC) count, we confirmed that in 129 adult patients with untreated CD the mean percentage of PC (4.9 (7.8)% was significantly higher (p<0.001) than that of 20 healthy controls (0.8 (0.7)%), and lower (p<0.001) than that of 20 subjects

The British Society of Gastroenterology

Assessment of prevalence, familial occurrence, and possible factors inducing splenic hypofunction in adult coeliac disease in Italy

G R CORAZZA, I AMOROZA, A STROCHI, G ZOLI, W MANTOVANI, AND G GASBARRINI (I Patologia Medica, Policlinico S Orsola, University of Bologna, Italy) Recent studies have shown that in Ireland the prevalence of splenic hypofunction (SH) is 76% in patients with untreated CD and 20% in their first degree relatives. Using the same method to evaluate splenic function, based on the pitted cell (PC) count, we confirmed that in 129 adult patients with untreated CD the mean percentage of PC (4.9 (7.8)% was significantly higher (p<0.001) than that of 20 healthy controls (0.8 (0.7)%), and lower (p<0.001) than that of 20 subjects
who had undergone splenectomy (32-8 (7-8)%). However, only 42 of 129 (32-5%) untreated CD patients had PC values higher than the upper limit of the control range (4%) and were considered to be hypoplastic. Moreover, PC counts from 50 first degree relatives (mean 0-7 (0-4)) did not differ significantly from those of healthy controls, and no relative had a PC >4%. It has been suggested that the presence of HLA DR3 can, by itself, be a predisposing factor to SH, but PC values of HLA DR3 positive untreated CD patients (mean 4-5 (6-1)%) did not differ from those of HLD DR3 negative untreated CD patients (mean 4-0 (8-4)%). The influences of the covariates - age at diagnosis, malnutrition assessed as reduced % of ideal body weight, and severity of jejunal lesions morphometrically assessed as surface: volume ratio - on SH were estimated by multiple linear regression analysis. Only age at diagnosis was significantly associated (p<0-01) with the degree of SH.

This study shows that in Italy the prevalence of SH in CD and the influence of genetic determinants are less than in Ireland and this constitutes a new and important heterogeneity of CD. The duration of pre-exposure to gluten is a crucial factor for the onset of SH in CD.

Cardiovascular reflexes in coeliac disease: is autonomic neuropathy a complication?

D O'Mahony, T Croft, and M J Whelton (Dept of Gastroenterology, Cork Regional Hospital, Ireland) Neurological complications are well documented in coeliac disease (CD), with an incidence of 2% to 52% (mean 8%). Autonomic function has not been assessed in CD patients before. Autonomic dysfunction, if it occurred, might explain various symptoms such as postural dizziness, dry mucous membranes, impotence, diarrhoea despite absence of intestinal villous atrophy (VA). Relative hypnotension independent of weight, anaemia, and electrolyte abnormalities is a known feature of CD which could result from impaired baroreflex mechanisms.

We studied 45 randomly selected CD patients ranging from 13 to 75 years (16 men, 29 women) to compare autonomic function with a known group of controls with definite autonomic impairment in 1-6% (310 patients). We used the same protocol to assess parasympathetic (heart rate responses to Valsalva, deep breathing, standing) and sympathetic (blood pressure response to standing and sustained hand-grip) function. Three patients (6-7%) had definite autonomic impairment. Nine patients (20%) had one abnormal heart rate test. Definite impairment did not correlate with somatic nerve conduction abnormalities or VA on intestinal biopsy.

Definite autonomic impairment may occur in CD and may underlie some symptoms not explained by other means. It represents another aspect of neurological dysfunction in CD.

A mechanism for diarrhoea in alcoholism?

S Gore, M Gimirre, A J Morris, D Hill, S M Brownless, and H R Stockdale (Dept of Gastroenterology and Medical Physics, Royal Liverpool Hospital, Liverpool) The mechanism of diarrhoea in chronic alcoholism is unknown. We have investigated whether alcoholic patients with diarrhoea have altered small bowel transit. Twenty male alcoholics admitted for detoxification and 17 healthy male volunteers were studied. The alcoholic patients were studied within seven days of admission and had no evidence of concomitant small bowel disease. Gastric emptying was measured by external counting with a collimated crystal, after consuming a standard meal of sausages, baked beans, and mashed potato containing Technetium 99m labelled bran. Mouth to cecum transit time was measured by serial breath hydrogen analysis. No significant differences were found in gastric emptying rates between the normal subjects t½ (69 (34) min) (mean (SD)), and alcoholics with diarrhoea (57 (22) min) or without diarrhoea (77 (30) min). Mouth to cecum transit time of all the alcoholics was less than that of normal subjects (265 (73) and 307 (66) respectively) but not significantly so (p<0-05). The 11 alcoholics with diarrhoea, however, had a mean transit time of 234 (81) min, which was significantly shorter than the 10 patients without diarrhoea 304 (38) min (p<0-05).

These results show that the mouth to cecum transit time of a solid meal is shorter in alcoholics with diarrhoea than in those without. This reduction is not accounted for by more rapid gastric emptying. We conclude that alcoholics with diarrhoea have more rapid small intestinal transit.

Patients with a short bowel whose intestinal output exceeds oral intake need long term parental support

J M D Nightingale, J E Lennard-Jones, E R Walker, W R Burnham, and M J G Farthing (St Mark's Hospital, London and Oldchurch Hospital, Romford, Essex) In some patients with a short bowel, intestinal output is greater than oral intake whereas in others there is net absorption. This study aimed to show whether it is this factor that determines the need for long term parenteral fluids. Intestinal balance studies were performed in three groups of patients: group A, six patients (jejunal length 25-70 cm) needing long term intravenous nutrients, fluid, and electrolytes to maintain an adequate and stable nutritional status; group B, three patients (jejunal length 95-140 cm) needing long term parenteral fluid and electrolytes; and group C, six patients (jejunal length 20-120 cm) maintained on oral nutritional or electrolyte supplements, or both. Each patient chose a diet similar to that taken at home; this was given for two consecutive days. Measurements were made of oral intake and intestinal output including weight, sodium, potassium, and energy. In group A all patients showed a net secretory output in response to food (net balance -1.3 to -3.9 kg, sodium -169 to -332 mmol). In group B, two of three patients were in negative fluid and electrolyte balance. All patients in group C were in positive fluid and sodium balance (+1.6 to +2.4 kg, sodium +9 to +431 mmol). The difference between groups A and B was p<0-01 for both variables. Energy absorption was least in group A (1-11 to 34%), intermediate in group B, and greatest in group C (59 to 76%). A net secretory response to food determines if a patient with a short intestine will need parental support.

Double blind trial comparing elemental and polymeric diet as primary treatment for active Crohn's disease

R H Park, A Galldoway, B J Z Danesh, and R J Russell (Gastroenterology Unit, Royal Infirmary, Glasgow) Patients with active Crohn's disease (CD) may respond to elemental diet without any other form of treatment. We investigated whether this form of primary treatment was unique to elemental diets or found with polymeric diets. Fourteen patients with active CD requiring hospital treatment were allocated randomly to receive 2-4 l per day of elemental diet (ED), elemental diet (n=7), or polymeric diet (PD), enteral 400 l/day for 28 days via a nasogastric tube. Nutritional intake in all patients was similar. All other dietary intake was stopped and no patient was on immunosuppressive treatment. The diets
were delivered in their containers covered by a plastic sheet. Both groups were of similar age, duration of disease, and disease location. Disease activity was assessed before and after treatment by modified Crohn's disease index (MOD CDI), erythrocyte sedimentation rate, C-reactive protein, Inmun leucocyte scan, and gastrointestinal protein loss. There was no significant difference in pre-trial disease activity indices. Three ED patients and one PD patient failed to complete the trial due to increase in disease activity. After the trial the PD group's MOD CDI score was significantly better than the ED group (0.0-0.3 v 3.0-3.3) (median, range). p<0.05. There were no significant differences in the other indices. Nutritional parameters were similar for both groups. Five PD and two ED patients were in clinical remission at the end of the trial. Despite the apparent clinical remission, however, several laboratory parameters still indicated active disease in most patients. Patients who completed had relapse rates at one year of 100 v 66% (ED v PD) p>0.05.

There is no benefit in using an elemental diet in providing a remission in active CD. Longterm relapse rates are disappointing for both diets.

**Total parenteral nutrition via a central or peripheral line? A prospective and controlled clinical trial**

N COURSE, H JAEGER, I R PICKFORD, C J MITCHELL, J MACFIE (Scarborough Hospital, Scarborough, North Yorkshire) Many recent studies have reported successful total parenteral nutrition (TPN) administered via the peripheral route in carefully selected patients. It remains unclear, however, what proportion of all patients who require TPN are suitable for peripheral feeding.

We report a prospective trial in which 50 patients were randomised to receive TPN via either a central (CVP) or peripheral line (PPN). TPN was not possible in three patients who were classified as treatment failures (12%). In the remaining 22 patients a total of 270 days of TPN was given (mean (SD): 0.25 (0.2) g N/kg/day; 38 (4.3) kcal/kg/day). Minor complications occurred in nine patients (41%). A PPN was not possible in six patients (24%) as a result of poor peripheral veins in four and specific nutritional requirements in two. In the remaining 19 patients, a total of 161 days of TPN was given (0.22 (0.2) g N/kg/day and 33 (4.2) kcal/kg/day). These patients had a mean duration of feeding of 8.5 (4.2) days with 2.2 (1.3) line changes.

**Intestinal diamine oxidase deficiency in urticaria**

K HINUMA, M H LESSOF, V GANT, M MAGHSOUDI, G M MURPHY, AND R H DOWLING (Gastroenterology Unit and Div of Medicine, Guy's Campus, London) The enzyme diamine oxidase (DAO), formerly called histaminase, plays important roles in polyamine and histamine catabolism. It is almost exclusively confined to the intestinal mucosa, but can be released into the circulation by low dose (5000 U) intravenous heparin. Patients with chronic idiopathic urticaria are intolerant of intravenous histamine and degrade it more slowly than control subjects. It is not known, however, if urticaria patients have a deficiency of intestinal mucosal DAO. Therefore, we measured post-heparin plasma DAO profiles in 17 controls and 18 patients with chronic (>three months) recurrent (>five attacks) urticaria. The median two hour area under the curve (AUC) in the patients (16.9 mU/l/h) was significantly (p<0.002; Mann-Whitney) less than that in the controls (30.0). Seven of the 18 patients had little or no rise in plasma DAO after the intravenous heparin and no overlap in AUCs with the controls. Six of the 18 consented to peroral biopsies. Four had virtually no mucosal DAO activity (0.7-1.2 mU/g mucosal protein), two (16 and 53 mU/g) overlapped with the control values (median 18.5 mU/g; n=10).

Some, but not all, patients with chronic urticaria have intestinal DAO deficiency. Reduced intestinal DAO activity may be responsible for the impaired histamine metabolism in these patients. Thus patients with urticaria may have a newly recognised primary intestinal disease.

**Trophic effect of dietary peptides on the rat intestinal tract**

G K GRIMBLE, V R PEEDEY, P J GARLICK, AND D B A SILK (Central Middlesex Hospital and King's College Hospital, London and Rowett Research Institute, Bucksburn, Aberdeen) Diets containing protein or an equivalent free amino acid mixture promote equal weight gain in the growing rat. It is therefore assumed that absorption of the two forms of nitrogen is complete in the normal small intestine. However, colonic fermentation of malabsorbed protein may represent an important mode of assimilation of dietary nitrogen. The aim of the present study was to determine the relative effects of two elemental diets on growth patterns and the composition of peripheral and visceral tissues of the young growing rat.

Two powdered diets were prepared, differing only in the nitrogen moieties. One contained a partial enzymic hydrolysate of milk protein (PEP), whilst the other contained an equivalent free amino acid mixture (AA). Some 70 g male Wistar rats were fed, ad lib for 14 days and all tissues were weighed and assayed for RNA, DNA, and protein (mg/100 g BW).

Intake and weight gain were identical in both groups. Differences in weight (g), RNA, DNA, and protein were found only in cecum and colon (PEP v AA; p<0.05 or less, mean (SEM) Cecum - Weight: 0.70 (0.08 v 0.47 (0.09), DNA: 4.81 (0.22) v 2.70 (0.17), RNA: 3.28 (0.18) v 2.12 (0.15), Protein: 78.0 (4.5) v 53.4 (4.1) Colon - DNA: 3.17 (0.10) v 2.45 (0.07), Protein: 47.7 (1.3) v 42.9 (1.4).

The two diets seemed to have equal nutritional value. However, the PEP diet was trophic to the cecum and large intestine, compared with the AA diet. Two explanations seem possible. PEP may have contained peptides which were poorly absorbed and which stimulated the growth of the large intestine. Alternatively, nitrogen in the PEP diet was less well absorbed than from the AA diet, such that fermentation of the malabsorbed fraction in the large intestine exerted a similar effect to that observed with malabsorbed carbohyd-rate and dietary fibre.

**Return of normal interdigestive myoelectric complex cycles after total denervation of the jejunum**

E M M QUIGLEY, A D SPANTA, S G ROSE, J LOI, AND J S THOMPSON (Dept of Internal Medicine and Surgery, University of Nebraska Medical Center and Omaha Veterans Administration Medical Center, Department of Surgery, Methodist Hospital, and Swanson Center for Nutrition, Omaha, Nebraska, USA) The technique of autotransplantation (AT) permits study of the effects of total extrinsic denervation on intestinal function. Our aim was to study the
longterm effects of AT on the interdigestive myoelectrical complex (IMC).

Autotransplantation of the entire ileo-jejunum was performed in 12 adult female dogs and electrodes placed at intervals along its length. The IMC activity was studied from one to 20 months after AT.

Results: (1) IMC Organisation. Recordings within two months of AT showed complete absence of spike activity. From 5 to 10 months, disorganised IMC activity was evident; phase III complexes arising amidst periods of either prolonged quiescence or continuous phase II-type activity. From 10-15 months 40% of IMC cycles featured sequential phase I, II, and III activity, and by 20 months 88% of IMC’s were organised in normal sequence. (2) Phase III complexes. From 0-6 months only 25% of Phase III complexes occurred at regular intervals and propagated over at least 3/4 of the AT segment; between 12-20 months this proportion had increased to 83-3%. (3) Abnormal patterns. These included rapidly propagated spike clusters (incidence; m/m AT 1-6 months v AT 6-12 months v AT 12-20 months: 0·31 (35) v 0·24 (0·29) v 0·41 (0·48), ‘simultaneous’ phase III-type bursts, periods of rapidly propagated individual spikes, and isolated non-propagated phase III-type bursts.

We conclude that the denervated intestine can organise and propagate all phases of the IMC; this motor pattern is intrinsic to the intestine.

Rapid and simultaneous determination of lactulose and mannitol in urine using high pressure liquid chromatography

S C Fleming, M S Kapembwa, G E Levin, and G E Griffin (Dept of Communicable Diseases, St George’s Hospital Medical School, London) Aim: To produce a rapid and simple method for the determination of carbohydrates in urine for use in studies of intestinal permeability. Current methods of analysis include thin layer chromatography (TLC), gas chromatography (GC), and enzymatic, which may be time consuming and may require prior derivatisation. We describe a high pressure liquid chromatography method for carbohydrate analysis that overcomes these problems.

Urine is diluted between 1:2:5 and 1:20 with deionised water and added to the internal standards arabinose and cellobiose. The mixture is desalted with Aemolite resin (1R20H + IRA400C1), centrifuged and filtered. The filtrate (50 μl) is injected onto a Dionex HPIC-AS6 column. Carbohydrate is detected by pulsed amperometric detection, using 0.15 M NaOH as clutant at 1 ml/min.

Recovery is between 90% and 100-7% for all sugars. Lactulose and mannitol are separated from other carbohydrates commonly found in urine, within 15 min. The method is linear up to 500 μg/ml and has a sensitivity better than 0.5 μg/ml.

Sample preparation is both simple and fast. Lactulose and mannitol can be measured simultaneously. Retention times are low, thereby leading to a fast analysis time. The method is also applicable for the determination of other carbohydrates in biological materials.

Cisapride increases stool frequency without causing faecal losses of water, fat, and bile acids

V Berber, U Armbruch, A Heusinger, M Winkel, and B Stockbrügger (Marbach-Klinikum und Laborkliniek, Bad Kissingen and Zentrumklinikum Augsburg, Germany) To elucidate whether the increased stool frequency during cisapride treatment (C) is a consequence of malabsorption of water, fat, and bile acids caused by shortened small intestinal transit time, 12 healthy volunteers were treated with either tablets placebo qid (P) or tablets cisapride 10 mg qid (C) during two periods of five days each, in a double blind cross over study.

Stool frequency, stool consistency, and side effects were recorded each day. During the last 72 hours of each study period total faecal mass, faecal water content, and faecal excretion of fat and bile acids were determined.

Mean daily stool frequency was 18·8% higher during C treatment (p<0·01) than during P treatment (p=0·038). The stool consistency score increased by 11·8% towards softer stools during C (ns). There were no significant differences between total faecal mass (P: 399±3 g/72 h; C: 41·4±5 g/72 h), faecal water content (P: 75±6%; C: 76±2%), or faecal excretion of fat (P: 12±4 g/72 h; C: 11±6 g/72 h) and total bile acids (P: 2212 μmol/72 h; C: 2261 μmol/72 h). Side effects reported during treatment P were constipation (n=3), and during treatment C meteorism (n=4) and loss of appetite (n=2).

The increased stool frequency during C treatment is not caused by malabsorption of water, fat, or bile acids, but seems to be the consequence of a direct motor effect.

Effect of bolus doses of fat on small intestinal mucosal cell proliferation

P Jenkins and R F H Thompson (Gastrointestinal Laboratory, Bayne Institute, St Thomas’ Hospital, London) Bolus doses of ingested fat stimulate colonic mucosal cell proliferation more than divided doses, but the effect on the small intestine is unknown.

Two groups of eight female Wistar rats (200-220 g) were isocalorically fed an elemental diet giving 5·3 g glucose and 2·7 g amino acids/rat per day. Efamol, an oil rich in polyunsaturated fatty acids, was given to each group (3 ml/rat per day), either by gavage (1·5 ml twice daily) or mixed with the elemental diet consumed over 24 hours. After 21 days arrested metaphases were counted two hours after intraperitoneal vincristine at points 0%, 33%, 66%, and 100% small intestinal distance. The small intestines were divided into three equal segments and the mucosa weighed.

Body weight gain was similar for both groups. Overall small intestinal mucosal weight was greater after bolus than gradual fat ingestion (mean (SEM) 1·215±0·160 v 1·213±0·160, p<0·01), caused by changes in each segment. Bolus dosing increased cell proliferation (metaphases/two hours) at 33% (55·38±1·63) v 45±29 (1·30, p=0·001), 66% (41·28±3·01) v 30±78 (0·94, p=0·005), and 100% (27·49±1·83) v 21±82 (0·74, p=0·02) but less so at 0% (52·8±3·12) v 48±20 (2·60, ns).

Bolus fat ingestion increased small intestinal mucosal proliferation compared with equivalent doses consumed gradually over 24 hours. Thus the method of administering high fat diets influences the response of the small intestinal mucosa.

Intestinal luminal somatostatin and met-enkephalin-like immunoreactivity in response to prostaglandin E₁ and man

Sobhani, N Vidoon, A Radot, B Huche, and J C Rambaud (INSERM U 290, Hôpital St Lazare and INSERM U 10, Hôpital Bichat, Paris, France) Prostaglandins (PGs) E₁ and D₂ are known to regulate gastric secretions and to stimulate secretion of water and electrolytes in the jejenum. Somatostatin (SOM) and enkephalins (ENK) may also interact in these secretions. In order to investigate both peptide and fluid secretions during PG administration, we studied, in six healthy male volunteers (aged 22 (2) yr), the effect of PGE₁ on intraluminal SOM and met-ENK release, using a four lumen tube
with a jejunal proximal occluding balloon through a 40 cm long segment. The basal solution, isotonic to plasma (NaCl 130 mM, KCl 5 mM, mannitol 30 mM, PEG 4000 5 g, pH 7, per litre) was infused at a constant rate of 10 ml/min immediately below the balloon. After a basal period, PGE$_2$ (0-10 μg/kg/min) was added. Samples were collected in the presence of an enzyme inhibitor, and were frozen at −20°C until peptide radioimmunoassay. Immunoreactive SOM and met-ENK were determined by RIA’s based respectively on S$_{14}$ and met-ENK antibodies.

The differences between PG and basal movements, ∆H$_2$O, ∆Na+, and ∆K+ were 3-4 (0-3) ml/min, 494 (54) μmol/min, and 15-9 (1-8) μmol/min, respectively. The SOM output in the perfused segment did not vary significantly between the basal (57-3 ng/min) and the PG (41-6 ng/min) periods. On the contrary, there was a significant (p<0-01) decrease of met-ENK output during PG (48-5 ng/min) compared with the basal period (57-5 ng/min).

In man, somatostatin and met-ENK are present in jejunal juice. PGE$_2$ does not modify somatostatin secretion in the lumen, but significantly decreases intestinal met-ENK output suggesting regulation by PG of the intraluminal peptide releases.

Gut lavage: a new approach to the study of intestinal humoral immunity

S O'MAHONY, J R BARTON, S CRICHTON, AND A FERGUSON (Gastro-Intestinal Unit, University of Edinburgh and Western General Hospital, Edinburgh) Direct investigation of gut mucosal immunity requires the collection of intestinal secretions or mucosal biopsies, or both. We have evaluated a technique of whole gut lavage with a polyethylene glycol (PEG) electrolyte solution, a non-invasive means of obtaining material for study of gastrointestinal humoral immunity. The procedure was technically successful, with clear lavage fluid passed per rectum, suitable for immunoglobulin assay, obtained in 75 of 78 patients. The PEG assay in the lavage fluid of 25 patients showed that after passage through the gastrointestinal tract, there had been a uniform dilution (around 20%) of the ingested fluid. Lavage fluid immunoglobulins were assayed by enzyme-linked immunosorbent assay (ELISA). Appreciable loss of immunoglobulin due to sample deterioration could be prevented by prompt addition of protease inhibitors. Analysis of serial lavage specimens showed little variation in immunoglobulin content. Lavage fluid immunoglobulins in 20 immunologically normal volunteers were (mean (SD)) lgA: 101 (87-3) μg/ml (range 13-6-273-9); lgM: 8-3 (0-2) μg/ml (0-35-8); and lgG: 0-83 (0-75) μg/ml (0-00-2-13).

This method of gut lavage is not only an effective bowel cleanser but also a non-invasive and reproducible method of obtaining human intestinal secretions for study of immunoglobulin and antibody content.

Investigating gut mucosal immunity: direct study of gut secretions is mandatory

J R BARTON, S O’MAHONY, AND A FERGUSON (Gastro-Intestinal Unit, University of Edinburgh and Western General Hospital, Edinburgh) Many workers study antibodies in saliva on the assumption that data derived from the assay of this easily obtained secretion are applicable to the gastrointestinal tract as a whole. We have tested this hypothesis using whole gut lavage fluid as a reference material against which saliva and serum have been compared. ELISA was used to measure total immunoglobulin concentrations and specific antibodies to three common dietary antigens of the IgA, IgM, and IgG classes in lavage fluid, saliva, and serum of 20 healthy subjects.

No correlations between saliva and lavage fluid concentrations of IgA or IgM existed, although a positive correlation was found for IgG (r=0-452, p=0-03), which was present in trace amounts in the secretions. Antibody titres in saliva and intestinal fluid did not correlate for any isotype. In the case of IgM however, comparison of saliva with serum and lavage with serum showed significant positive correlations (saliva v serum antigliadin r=0-31, p=0-011, antiova r=0-49, p=0-001; lavage v serum antiova r=0-6, p=0-013).

This study suggests that saliva does not reflect immune events in intestinal secretions, that the gut must be studied directly, and that regulation of IgM antibody may not be segregated with respect to mucosal and systemic compartments, in contrast with IgA antibodies as is clearly shown.

Longterm somatostatin analogue is effective treatment in patients with APUDoma-related syndromes

J S COLLINS, K D BUCHANAN, C F JOHNSON, C SHAW, AND A VARGHESE (Dept of Medicine, The Queen’s University of Belfast, N Ireland) We have recorded our experience over 4 years in the use of somatostatin analogue (SMS) treatment in a series of rare APUDoma-related syndromes. All patients were treated on a named basis. Twenty four patients with 26 syndromes have been treated. Fifteen of these had the carcinoid syndrome (CS), four gastrinoma, two insulinoma, two VIPomas, and three patients had miscellaneous tumour types. Eighteen patients received SMS treatment for longer than four weeks by subcutaneous injection continuously in doses ranging from 50 μg to 1000 μg daily. In CS patients, 70% reported improvement in diarrhoea, 58% in skin flushing, and 100% in wheeze. Pulmonary carcinoids showed a better response than those of mid gut origin. In three patients with Zollinger-Ellison syndrome, serum gastrin values were depressed, although other acid inhibitory drugs were the preferred long term treatment. Both VIPoma patients showed a maximal clinical response to small infrequent doses, with complete cessation of diarrhoea, but the insulinoma patients showed no response. Overall, side effects were confined to local skin discomfort at injection sites. Only one patient stopped treatment because of intolerable flatulence. No reducing effect was shown on tumour bulk and a negative correlation between tumour marker levels and clinical response was present.

Pancreaticobiliary posters

Interleukin 6 a mediator of the acute phase response in acute pancreatitis?

D J HEATH, A M CRUICKSHANK, A SHENKIN, AND C W IRMIE (Depts of Biochemistry and Surgery, Glasgow Royal Infirmary, Glasgow) Recent evidence suggests that the cytokine interleukin 6 (IL6) plays a part in mediating the acute phase response. To study the effect of IL6 in the changes in acute pancreatitis we measured the serum concentrations of C-reactive protein (CRP) and pancreatic secretory trypsin inhibitor (PSTI) (two acute phase proteins), and IL6 in 10 patients with acute pancreatitis.

Blood samples were taken six hourly for the first 48 hours and twice daily for a further three days. Specimens were stored at −20°C until analysis. The IL6 concentrations were measured using an in-house bioassay (1 IU representing approximately
Influence of alcohol on outcome of resection for pancreatic cancer

B A THEIS, S SHANKAR, AND R E G RUSSELL (Middlesex Hospital, London) It is usually stated that patients in whom alcohol is the cause of pancreatic disease do less well after surgical treatment. To determine if this is true, the outcome of 230 patients who had undergone resection (proximal 84, distal 98, total 48) was examined at 1, 3, and 5 years.

Some 104 patients had alcohol (A) as their prime aetiology and the remainder (R) had mixed causes (divisum 23, gall stone 22, trauma 19, hereditary nine). Comparisons were made for age, length of history, and operative morbidity, and mortality. The patients were followed in a special clinic for up to 10 years, and their status in terms of analgesic consumption, fitness for work, late mortality, and incidence of diabetes and steatorrhoea were compared.

There was no significant difference between the age (A 37, R 40 years), length of history (A 3; R 2 years), postoperative stay (A 20, R 20 days), or complications (A 54%, R 56%), but operative mortality was six in R compared with one in A. There were, however, 12 late deaths in group A, compared with seven in R. In the follow up period, no significant difference could be shown in severity of pain (A 26%, R 20%), narcotic consumption (A 14%, R 6%), or fitness to work (A 78%, R 86%).

The incidence of steatorrhoea, as determined by enzyme consumption, was similar (A 61%, R 56%), as was the incidence of diabetes (A 62%, R 53%).

We conclude that the results of surgery are similar in patients with pancreatitis whether or not the cause is alcohol.

Value of morphometry in predicting behaviour in pancreatic islet cell tumours

R D KENNY, J M SLOAN, P W HAMILTON, P C H WATT, E JOHNSTON, AND K D BUCHANAN (Depts of Pathology and Medicine, Royal Victoria Hospital, Belfast) Accepted histological criteria of malignancy are unreliable in pancreatic islet tumours. The purpose of this retrospective study was to examine the value of morphometry in predicting islet cell tumour behaviour.

Ten cytological variables were studied in 31 islet cell tumours using semiautomatic image analysis, without prior knowledge of tumour behaviour. Mitotic rate, gross tumour size, and hormone secretion were also assessed. Seventeen localised and nine metastasising tumours were initially examined. Discriminatory analysis identified the nuclear:cytoplasmic ratio and number of nuclei/mm² as the most useful features in distinguishing benign from malignant tumours. A classification rule based on these variables successfully classified 92% of cases. When this rule was applied to five further tumours all were correctly classified. Most insulin secreting tumours (94%) were benign while four of seven non-functional tumours metastatised. Most tumours secreting other hormones metastatised. Tumour mitotic rate was not a useful discriminatory feature. The mean gross diameter of malignant tumours was substantially greater but there was considerable overlap.

Morphometric analysis is not excessively time consuming when only two discriminatory features are identified and may be a useful addition to the histological assessment of islet cell tumours.

Does tamoxifen influence survival in pancreatic cancer? A randomised controlled clinical trial

O M TAYLOR, M J MCMAHON, AND E A BENSON (Dept of Surgery, General Infirmary, Leeds) It has been suggested that carcinoma of the pancreas is oestrogen sensitive, and tamoxifen treatment improves the prognosis. Patients from 14 hospitals in the Yorkshire region were recruited into a placebo controlled, double blind study of tamoxifen (20 mg bd). Entry criteria included positive histology and an unresectable lesion. Patients were staged using combinations of ultrasound, computed tomography, and laparotomy, and progress was assessed using the Karnofsky performance score and the Hospital Anxiety and Depression (HAD) score. All patients were followed up monthly, until death.

In an 18 month period, 102 patients with probable pancreatic adenocarcinoma were identified. The diagnosis was confirmed by biopsy examination in 59, and 44 patients were randomised. Tamoxifen was given to 19 patients and 20 received placebo. The groups were well matched for age, stage of disease, Karnofski and HAD scores, but there were more women in the placebo group (six v 11). Analysis of the survival of the two groups by life table suggested there was no significant difference (p = 0.3; Mantel Cox). Changes in Karnofsky and HAD scores were also similar, and apparently unaffected by tamoxifen.

This study suggests that tamoxifen is unlikely to have a major influence on the survival of patients with cancer of the pancreas, and casts further doubt upon the hormone dependence of the neoplasm.
Role of gastric phase in fat induced gall bladder contraction and cholecystokinin secretion in humans

A MASCLEE, J B MJ JANSSEN, W M M DRIESEN, I M GEUSKENS, AND C B H W LAMERS (Dept of Gastroenterology, University Hospital Leiden, Dept of Internal and Nuclear Medicine, St Joseph Hospital, Eindhoven, The Netherlands) The present study was undertaken to determine the role of the gastric phase in gall bladder contraction and cholecystokinin (CCK) secretion.

We compared the effect of intragastric v intraintestinal administration of 60 ml corn oil on gall bladder emptying (by cholescintigraphy) and CCK secretion (by RIA) in eight healthy subjects and eight patients with partial gastrectomy in whom gastric emptying is known to be accelerated. In healthy subjects, intragastric fat resulted in a significantly (p<0.05) later rise in plasma CCK (20 (2) min) and onset of gall bladder emptying (20 (2) min) compared with intraintestinal fat (5 (1) min and 10 (1) min, respectively). Plasma CCK and gall bladder responses to intragastric fat were significantly (p<0.01) reduced during the first 30 minutes after stimulation when compared with intestinal fat. In patients with partial gastrectomy, the rise in plasma CCK (10 (1) min) and the onset of gall bladder emptying (10 (1) min) were in the same range after intragastric and intraintestinal fat. No significant differences in plasma CCK or gall bladder responses were found according to the site of fat application.

In conclusion, plasma CCK and gallbladder responses to intragastric fat are significantly delayed in healthy subjects, compared with patients with partial gastrectomy, probably because of differences in gastric emptying. The main role of the stomach in the regulation of gall bladder contraction is by rating the delivery of the stimulus to the intestine.

Simplifying measurement of gall bladder function with ultrasound

J S BESWICK, P M HUGHES, AND D J MARTIN (Dept of Radiology, Gastroenterology Unit, University Hospital of South Manchester, Manchester) A functioning gall bladder is necessary for non-surgical management of gall bladder stones. We have evaluated an ultrasound method of assessing gall bladder function in 42 normal volunteers and 19 gall stone patients. Gall bladder volume (GBV) was measured after fasting and at 15 minute intervals after ingestion of a standard fatty meal. In normal volunteers, resting GBV was 19-4 ml, mean maximum ejection fraction was 64%, mean time to maximum ejection was 47 min and the emptying rate was 0.4 ml/min. Intraobserver error was 7.2% and interobserver error 9.8%. In 19 gall stone patients, nine of whom had a cholecystogram (OCG), seven showed no contraction on ultrasound and a fasting GBV of 20.3 ml. (Four had OCG, all non-opacifying.) In 12 showing emptying on ultrasound (five had OCG, all opacifying), the fasting GBV was 29.5 ml, mean maximum ejection fraction was 55.7%, mean time to maximum ejection was 61 min, and the emptying rate was 0.4 ml/min.

Ultrasound is simple and reproducible and can assess gall bladder contraction and hence cystic duct patency, showing good correlation with OCG. Radiological assessment of patients for non-surgical management of gall bladder stones can be limited to fasting GBV, one hour post fat GBV, and CT to assess stone density. All examinations can be performed during one visit to the radiology department.

Percutaneous treatment options in benign biliary disease

A GILLAM, S MATHER, W TAYLOR, J S DOOLEY, AND R DICK (Depts of Radiology and Medicine, Royal Free Hospital and School of Medicine, London) Patients with symptomatic benign biliary strictures in whom surgery is not considered appropriate, and in whom an endoscopic approach is not possible are a difficult treatment group. We have treated 21 of these patients (eight men, 13 women; mean age 56 years, range 23-82) with either percutaneous balloon dilatation (PD) or insertion of an endoprosthesis, made either of plastic (PE) or metal (ME). Strictures were postoperative in 17, idiopathic in three, and due to primary sclerosing cholangitis in one. In 16 of the patients a total of 28 corrective biliary operations had been performed. The indication for the percutaneous procedure was recurrent cholangitis with or without jaundice. Seven patients had PD, eight PE, and seven ME (total 22 procedures). One patient had a PE followed 22 months later by an ME. Five patients developed early complications (PD: 2; PE: 1; ME: 2). The median asymptomatic period after the procedures was: PD 12 mths (range 10-30 mths), PE 14 mths (range 4 mths-8 yrs), and ME 10 mths (range 6-16 mths). Recurrent symptoms necessitated a further procedure (or surgery) in: PD five of seven; PE four of eight; ME three of seven, at a median of 12 mths, 19-5 mths, and 11 mths respectively.

Patients in all groups achieved a valuable period of biliary drainage. A further procedure was needed, however, in 57% 9 mths-5 yrs later. Patients with PE had a longer symptom free period. Despite advances in technique and equipment it is not yet clear which approach is best.

Endoscopic endoprosthesis for malignant biliary obstruction

G I CULLINGFORD, R SRINIVASAN, AND D J CARR-LOCKE (Dept of Gastroenterology, Leicester Royal Infirmary, Leicester) Endoscopic endoprosthesis insertion (EPI) for malignant biliary obstruction offers palliation of jaundice either before surgery or as an alternative to it. This review is of 114 consecutive patients (59 men, 55 women), mean age 71-3 years, with malignant biliary obstruction who underwent 158 attempts at EPI between 1982 and 1988. Eighty one (71%) had obstructions below the cystic duct insertion and 33 (29%) above. Ninety four patients (82%) had successful EPI on 124 (78%) occasions. Sphincterotomy was performed in 62 (66%) patients. There were 34 failures of EPI, 23 due to inability to pass the guidewire, six from poor patient compliance, and five from failure to pass the endoprosthesis (EP) despite correct guidewire position. There were 20 (12%) procedure related complications after the 158 endoscopic retrograde cholangiopancreatographies (ERCP). Five (4-4%) were fatal: two with peritonitis and three with hepato renal syndrome. Cholangitis occurred after 7.3% EPI and 14.3% were failures. The 30 day mortality was 23 (20-2%). Twenty seven patients had surgery after ERCP, seven (four with resectable tumours) after successful EPI with improvement of liver function tests (LFT), 14 for failure of EPI or LFT improvement, five (4-4%) for gastric outlet obstruction, and one with bile peritonitis. An EP exchange was required in 21 (18-4%) patients (30 occasions) after a median time of 3-6 months. One hundred and two (89-5%) patients have died, with a median survival of 16-3 weeks. EPI relieved the jaundice in 77 (83%) of the 93 patients with EPs in situ for more than 30 days.

EPI provides a safe alternative to palliative surgery for malignant biliary obstruction.

Should distinction be made between primary and secondary sclerosing cholangitis?
Fish oil prevents cholesterol crystal formation and development of gall stones in mice

J Moore, B Banerjee, and E Singh
(University of Connecticut Health Center, and Newington VA Medical Center, Farmington and Newington, Connecticut, USA)

Fish oils are rich in omega 3 fatty acids that have effects analogous to non-steroidal anti-inflammatory agents (NSAIDs), which prevent gall stones. We tested the hypothesis that a diet including fish oil would prevent gall stone formation in mice fed a lithogenic diet.

We gave retared breeder female mice pelleted food containing 1% cholesterol and 0.5% cholic acid. In half the mice, the food also contained fish oil 30%, and in the other half, corn oil. Cholesterol crystal formation was observed in animals killed at two weeks by examination of gall bladder contents by polarised light microscopy. Cholesterol gall stone formation was measured in animals killed at eight weeks by centrifugation to retrieve buoyant cholesterol, and the digitonin assay. At two weeks only one of the six animals that had received corn oil had fewer than five liquid cholesterol crystals per gall bladder, while only one of six who had received fish oil had more than five liquid crystals per gall bladder (p<0.05). At eight weeks the mean (SD) content of solid cholesterol per gall bladder was: 47 (30) μg in the corn oil fed animals, and 9 (9) μg in the fish oil fed animals (n=16 in each group, p<0.001).

Fish oil prevents the formation of cholesterol crystals and the development of cholesterol gall stones in mice fed a lithogenic diet.

Routine computed tomography (CT) screening for calcification in gall stones significantly improves outcome of oral dissolution treatment

J F Walters, K A Hood, A Keighley, G M Murphy, and R H Dowling (Gastroenterology Unit, United Medical and Dental Schools, Guy’s Campus, London) Patients with cholesterol gall stones may be effectively treated using a combination of chenodeoxycholic acid (CDCA) (7 mg/kg/day) and ursodeoxycholic acid (UDCA) (5 mg/kg/day) each at half their monotherapeutic dosage. We have used this combination in a prospective study over the past five years of 54 patients with radiolucent stones, but have obtained complete dissolution in CDCA, and have obtained complete dissolution (CD), defined as two normal ultrasound scans, in only 42 (2) (SE)% after 24 months. At 12 months, CD was present in 23 (1)% and partial dissolution (PD) in 61 (2)%.

We have recently shown that ~50% of radiolucent stones are composed of cholesterol and calcium, which will limit the success of oral dissolution treatment. Consequently, in the past three years we have performed routinely a CT of the gall bladder region, and those patients with stone CT-density >100 HU have not been treated. Patients screened by CT (n=23) had significantly better dissolution rates (SE)% than those not screened (n=29). By 18 months, stone CT-density was 67 (9)% of patients selected after CT screening v 23 (2)% of those not screened. The CD rates at 12 months were 34 (4)% v 18 (2)%, while PD at 12 months was 82 (10)% v 49 (3)%. Median stone size and number were similar in both groups.

Routine CT before treatment is recommended as an effective way of selecting those patients with gall stones most likely to respond to treatment with UDCA and CDCA.
for the identification of a high risk population to guide better management. Septicaemic shock was present in 35 patients before surgery. All patients had ductal exploration under general anaesthetic. Additional procedures included cholecystectomy (n=55), cholecystostomy (n=5), and transhepatic intubation (n=2). Complications or death occurred in 43 (50%) and 17 (20%) patients respectively. Multivariate analysis on the 25 clinical (n=14) and biochemical (n=11) parameters evaluated yielded five risk factors (relative risk): (1) the presence of concomitant medical problems (4-5); (2) pH<7-4 (3-5); (3) total bilirubin >90 µmol/l (3-1); (4) platelets <150x10^9/l (2-9); and (5) serum albumin <30 g/l (2-9). Among patients with three or more risk factors, postoperative morbidity and mortality were 91% and 55% respectively – significantly higher than those with two or fewer risk factors – 34% (p<0.001) and 6% (p<0.001) respectively.

While routine application of nonoperative biliary drainage for all patients with SAC is probably unnecessary, this option might be considered for the selected high risk population.

Computed Tc99m HIDA scanning and bile crystal analysis in the investigation of suspected acalculous gall bladder dyskinesia

M Winslet, C Hall, K Harding, A Bignall, and J P Neoptolemos (Depts of Surgery, Nuclear Medicine and Clinical Chemistry, Dudley Road Hospital, Birmingham)

Although the detection of gall stone associated gall bladder disease is relatively straightforward using conventional radiology, conditions with a functional aetiology may not be detected. Tc99m HIDA is used conventionally for imaging in acute cholecystitis. In a modified dynamic mode it may be used to identify biliary dyskinesia in patients with abdominal pain of unknown origin.

Eleven patients (three men and eight women, mean age 54 (32–76) y) with undiagnosed upper abdominal pain (median duration 48 (4–120) months) were studied. LET's were abnormal in four (AsT=3, AIk P=1). Ultrasound and endoscopy were normal (n=11), as was oral cholecystography (n=2). Endoscopic retrograde cholangiopancreatography was normal in nine and failed in two. Bile crystal analysis was positive in two, negative in eight, and failed in one. Dynamic HIDA scanning was negative in three but showed dyskinesia with poor filling (n=4) or emptying (n=4) or both in eight. The ejection fraction was reduced (mean=25%, controls=40% + 10%).

Seven patients underwent cholecystectomy and one awaits surgery. Histology showed chronic cholecystitis alone in two with cholesterosis in five. All remain asymptomatic at median follow up of 6 (3–12) months.

Dynamic HIDA scanning may be used to identify biliary dyskinesia in patients with upper abdominal pain or unknown origin.

The false security of aerobilia

A Gyllens, R Dick, G Rubin, and J S Dooley (Depts of Radiology and Medicine, Royal Free Hospital, London) Air in the biliary tract (aerobilia) is seen after endoscopic sphincterotomy and surgical biliaryenteric anastomosis, or, rarely, may be produced in situ by gas forming organisms. When aerobilia is seen in the absence of severe sepsis, it is often assumed that there is no biliary obstruction. We present a group of patients with aerobilia and biliary obstruction.

Six patients (four men, two women; mean age 44 years) with previous biliaryenteric anastomoses presented with a history of cholangitis and jaundice (median bilirubin 67 µmol/l; range 21–362). Restructuring was suspected and investigation with noninvasive imaging – plain x-ray, ultrasonography, or computed tomography – was performed. One or more investigations showed aerobilia. Cholangiography showed an obstructing stricture at the anastomosis requiring treatment in all patients. Cultures of bile, available in five of the six patients, did not yield gas forming organisms. Gas in the biliary tree, in the absence of gas forming organisms, does not necessarily mean bile duct/anastomotic patency. Cholangiography is still indicated. Air crosses even very tight strictures in sufficient quantities to be radiologically detectable.

Do patients need cholecystectomy after endoscopic sphincterotomy for bile duct stones?

D Vair, C C Ainsley, B Theis, S J Williams, A C Smith, A Romanos, D Avanidius, J F Dowsett, R C G Russell, and A R W Hatfield (Depts of Gastroenterology and Surgery, Middlesex Hospital, London) As endoscopic sphincterotomy and clearance of common bile duct stones is being increasingly performed in younger patients and in those with gall bladders (GB) in situ, it is becoming more important to decide whether to proceed to elective cholecystectomy. At the Middlesex Hospital between 1983 and 1988, endoscopic sphincterotomy was attempted in 481 patients (240 men, 277 women; mean age 76-2 years) with GB in situ and radiologically confirmed bile duct stones at endoscopic retrograde cholangiopancreatography. Complete follow up (mean 36-2 months, range 1–61) is at present available for 295 patients.

Stones were clearly identified in the GB in 188 (63-7%) patients, while in 107 none were seen. After endoscopic sphincterotomy, 265 (90%) patients had either successful duct clearance or long term endoscopic drainage with pig-tail stents. Surgery including cholecystectomy was performed in 23 of 30 endoscopic failures. In the remaining 162 patients with GB stones, 40 had a subsequent cholecystectomy. In 24 patients (14-8%, mean age 65-4 years) cholecystectomy was for symptoms caused by GB stones, while in 16 asymptomatic patients (10%, mean age 63-8 years) cholecystectomy was undertaken electively on medical advice. In contrast, none of the 107 patients without GB stones required cholecystectomy (p<0.001).

In most patients with gall bladder stones, endoscopic sphincterotomy and the clearance or drainage of the bile duct represents definitive treatment. Subsequent cholecystectomy due to symptoms is necessary in less than 15% of patients. No patients without GB stones required a subsequent cholecystectomy.

Needle-knife precut papillotomy for sphincterotomy and cholangiography

D F Tweedle and D F Martin (Depts of Surgery and Radiology, Gastroenterology Unit, University Hospital of South Manchester) Needle-knife precut papillotomy (NKP) is an acceptable technique to facilitate endoscopic sphincterotomy (ES) when cholangiography shows disease, but its use to achieve cholangiography when common duct cannulation has failed has not been emphasised. Between 1985 and 1987, 63 patients had NKP. In 24 (22 stones, two tumour) cholangiography was achieved but ES failed. After NKP, ES was achieved immediately in 13. Three patients developed complications but recovered with conservative treatment. Eleven patients underwent delayed ES (mean 33 days after NKP) without complication. NKP was performed because of failure to...
obtain a cholangiogram in 39 patients with clinical and radiological bile duct obstruction. In two with tumour, cholangiography failed after NKP, and both patients died from progressive disease. Cholangiography was achieved immediately in 27 and at repeat endoscopic retrograde cholangiopancreatography in 10, and allowed endoscopic relief of obstruction. Complications developed in one patient who suffered cholangitis after failure to clear common duct stones. In five of the 39 patients no pathology other than bile duct dilatation was shown by NKP-assisted cholangiography. The value of NKP for assisting ES is confirmed and is without increased risk. In addition, the value of NKP to obtain a cholangiogram in selected patients and allow endoscopic treatment, is emphasised.

**Monoctanoin inhibits significantly in vivo gallstone dissolution by methyl-tert-butyl ether – an experimental study in the dog**

J. KEATING, E. O'REILLY, P. BURKE, J. MONSON, D. O'ROURK, A. CORRIGAN, R. STEPHENS, AND P. W. KEELING (Depts of Surgery and Gastroenterology, School of Pharmacy, Trinity College, Dublin) Although methyl-tert-butyl-ether (MTBE) is toxic, it dissolves cholesterol gall stones. In an in vitro study the addition of monoctanoin (MO) to MTBE in a ratio 25:75 produced more rapid dissolution of cholesterol gall stones compared with that produced by MTBE alone (MTBE: n = 10) vs MTBE + MO (n = 10): 26% vs 41% (p < 0.05). The addition of bile or water to the solvent systems slowed dissolution significantly.

In a preliminary study using four dogs where human cholesterol gall stones were placed in the animal gall bladder, an infusion of MTBE at 10 minute cycles in the presence of a patent cystic duct was associated with a 50% mortality in contrast with the Mayo Clinic data. In a subsequent in vivo study, 12 dogs were randomly allocated to receive either MTBE alone or the MTBE/MO mixture. Solvent was infused (10 ml in 45 minute cycles for five hours) via a catheter inserted into the fundus of the gall bladder containing three weighed gall stones. Bile was excluded by temporary occlusion of the cystic duct. The mean reduction in stone weight for MTBE (n = 18) was significantly greater than that achieved with MTBE/MO (n = 10): 83.8% (0–100%) vs 40–5% (0–57%), (p = 0.002) (median and range Wilcoxon's rank test). Solvent recovery was 65% with MTBE and 73% with MTBE/MO. There was no mortality.

The results show that while the in vitro addition of 25% monooctanoin to 75% MTBE causes rapid dissolution of gall-stones in a stirring system, it significantly reduced the in vivo efficacy of MTBE.

**ENDOSCOPY POSTERS**

**Anxiety levels before upper gastrointestinal endoscopy**

G. MASTROPAOLO, M. L. GHELPER, S. KUSSTATISHER, F. DI MARIO, AND R. NACCARATI (Cattedra Malattie Apparato Digerente, Università di Padova, Italy) Upper gastrointestinal endoscopy (UGIE) is regarded by patients as a most invasive examination. The use of sedatives beforehand is being debated, but very few data are available on the psychological effect of UGIE on patients. However, some of the cardiorespiratory changes observed during UGIE could be related to psychosomatic reactions. The aim of the present study was to evaluate anxiety levels in these patients. Some 137 outpatients (70 men, 67 women; 15–81 years) were tested for anxiety levels just before UGIE. Anxiety was assessed by two self-administered questionnaires (State–Trait Anxiety Inventory, Spielberg 1970), which assign a score (min 20–max 80 pt) to anxiety levels due to both the patient's personality and transient emotional states. Results were compared (Student's t test) with those of 91 outpatients (51 men, 40 women; 23–85 years) awaiting gastroenterological consultation only.

Trait anxiety was similar in the two study groups, but was higher in women (mean (SD) 45.2 (9.9)) than in men (40.5 (9.8)) (p < 0.001). In men, anxiety state levels before UGIE (42.4 (10.4)) were similar to those before consultation (43.0 (8.8)), but in women UGIE induced far more anxiety (49.8 (10.8)) than consultation (45.6 (10.4)) (p < 0.05). The difference between sexes was significant (p < 0.001). Patients undergoing their first UGIE (n = 60) showed similar levels of anxiety to those having followed up endoscopy.

UGIE is particularly stressful in women. Previous experience can reduce patient anxiety before a test, but this is not the case with UGIE, suggesting that it leaves an unpleasant memory. Mild sedation could be desirable for some patients, particularly those who may need further endoscopic examination.

**Prognostic importance – variceal white nipple sign (platelet-fibrin plug) in acute variceal bleeding**

S. SIRINO, P. A. MCCORMICK, P. MISTRY, G. KAYE, A. N. PHILLIPS, AND A. K. BURRAGUES (Academic Dept of Medicine and Clinical Epidemiology, Royal Free Hospital and School of Medicine, London) One report has described a platelet fibrin plug as a white nipple on top of a varix found during endoscopy in 10% of patients with variceal bleeding – the pathogenesis is uncertain, but it is believed to indicate impending bleeding. Our first case was represented by a bleeding spur which arose from a variceal cherry red spot and then spontaneously stopped bleeding to form a white nipple. We have prospectively evaluated endoscopically (and using a standardised protocol of management) 203 consecutive patients with cirrhosis admitted for variceal bleeding over 27 months, for the presence of a white nipple and its clinical associations particularly early rebleeding. In 18 (9–7%) we found a white nipple, but these cirrhotics did not differ significantly from the other 185 in terms of time to admission, time to endoscopy, sex, age, platelet count, severity of liver disease (Pugh's criteria), urea, haemoglobin, blood pressure, pulse, blood or plasma transfusion requirements, or previous episodes or treatment of variceal bleeding. There was also no difference in the numbers of patients in whom conservative measures failed who rebled within five days of admission; six of 18 (33%) vs 59 of 185 (32%), or in the time interval to failure. Mortality per patient admission was similar.

A white nipple sign in variceal bleeding is diagnostic of a varix which has recently bled but has no prognostic significance for impending rebleeding contrary to the letter in the literature.

**Comparison of chronic and demand sclerotherapy in poor risk patients with oesophageal varices**

R. F. MCKEE, O. J. GARDEN, I. PETTIT, J. R. ANDERSON, AND D. C. CARTER (University Department of Surgery, Glasgow Royal Infirmary) Although injection sclerotherapy is now well established as a means of treatment for oesophageal varices, debate continues about the details of treatment. Chronic sclerotherapy has been shown to improve survival when compared with conservative treatment alone, but it has been suggested that sclerotherapy only...
after variceal bleeds gives similar survival rates.

Forty consecutive patients who had survived an endoscopically proven variceal bleed within the previous week but were considered poor risks for surgical treatment (modified Child’s grade C or age 65 years) were entered into a prospective randomised study to compare planned chronic injection sclerotherapy (PS) with sclerotherapy only to treat variceal bleeding (demand sclerotherapy (DS)).

Some 22 patients were randomised to PS and received sclerotherapy at three weekly intervals until variceal obliteration was achieved. A further 18 patients were randomised to DS and were reviewed regularly as outpatients. In all patients, sclerotherapy was performed after any variceal bleed requiring blood transfusion. Follow up currently ranges from two to 36 months (mean 21-4).

Chronic sclerotherapy did not improve survival in this group but has almost halved the incidence of variceal bleeds.

Improving the use of upper gastrointestinal endoscopy

S A NAIJ, P W BRUNIT, S HAGEN, N A MOWAT, I T RUSSELL, T S SINCLAIR, AND T M TANG (Health Services Research Unit, University of Aberdeen and Gastro-intestinal Unit, Grampian Health Board, Aberdeen) We undertook a retrospective study to investigate how endoscopies yielding positive findings differ a priori from those yielding negative findings; and how those adjudged ‘helpful’ (in the sense of influencing management) differ a priori from those adjudged ‘unhelpful’. We sampled 483 patients undergoing endoscopy and abstracted a wide range of data, including 48 patient characteristics available to the gastroenterologist at the time of the decision to perform endoscopy.

Sixty nine per cent of endoscopies were positive. Discriminant analysis identified four variables which taken together were strongly predictive of positive endoscopy. The resulting discriminant function correctly predicted the outcome of 76%. Eighty two per cent of the endoscopies were retrospectively classified by the gastroenterologists as helpful. Six variables were strongly predictive of a helpful endoscopy. The corresponding discriminant function correctly predicted the outcome - of 84%.

Comparison of the two analyses shows that the two sets of predictions differ substantially. Thus it is important that decision making tools should be based, not on the crude distinction between positive and negative, but on the potentially more productive (though methodologically more difficult) distinction between helpful in influencing management and unhelpful.

Endoscopic submucosal injection of fibrin adhesive in peptic ulcer bleeding

O FRIEDRICH, J PAPEN, AND L BECCU (St Barbara Hospital, Duisburg and Bethesda Krankenhaus, Duisburg, FRG) The aims of our treatment in patients with bleeding peptic ulcers are: (1) stopping the haemorrhage definitively, (2) avoiding relapse bleeding, (3) avoiding emergency surgery, (4) avoiding all operations on high risk patients, and (5) initiating healing of the ulcer. The new method we use to stop haemorrhaging is to close the lesion using a submucosal fibrin gel. The adhesive, a thrombin and fibrinogen mix, is injected in the immediate vicinity of the bleeding lesion, forming the fibrin clot.

Our results in 250 bleeding patients grouped according to the Forrest-classification are: arterial n=15, ooze n=45, F II bleeding n=190 (among these were 96 patients classified II with a visible vessel). All bleeding was stopped immediately, but in four patients it was not possible to ‘fix’ the clot securely. One relapse haemorrhage occurred, but repeat fibrin gluing led to definitive haemostasis.

According to our results, submucosal fibrin adhesion is better than other endoscopic methods, since (1) it is not tissue destructive, (2) the ulcer is sealed, (3) primary healing is obtained, and (4) primary haemostasis equals definitive haemostasis. Restrictions of the application can arise when the bleeding source cannot be located precisely, and in these patients early selective operation should be considered.

Oral ciprofloxacin as antibiotic prophylaxis in patients undergoing endoscopic retrograde cholangiopancreatography

C G ALVEY, D A F ROBERTSON, AND R WRIGHT (Dept of Medicine II, University of Southampton, Southampton General Hospital, Southampton) Infection is an important complication in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). We have studied oral ciprofloxacin as a prophylactic agent in high risk patients (jaundiced or with radiological evidence of biliary obstruction) and low risk patients.

In a double blind, placebo controlled study 32 low risk patients (14 men, 18 women; mean age 55.3 years) were randomised to receive either ciprofloxacin 750 mg orally (n=16) or placebo (n=16) as a single dose at least 90 minutes before ERCP began. No infective complications were seen in either group.

In an open study 42 high risk patients (24 men, 18 women; mean age 70.4 years) were randomised to receive either ciprofloxacin 750 mg by mouth twice daily (n=21) or cephalosporin 1 g intravenously twice daily (n=21) for three days, beginning at least 90 minutes before the procedure. One patient receiving cephalosporin developed cholangitis and documented septicemia: there were no infections in the ciprofloxacin group.

One low risk patient developed a transient erythematous rash on ciprofloxacin; no other adverse reactions occurred.

Orally administered ciprofloxacin is an effective, well tolerated, and comparatively cheap agent for antibiotic prophylaxis in high risk patients undergoing ERCP, and compares favourably with a parenteral cephalosporin.

Upper gastrointestinal endoscopy in investigation of iron deficiency anaemia

M V TOBIN, W AHMED, A L MORRIS, AND I T GILMORE (Gastroenterology Unit, Royal Liverpool Hospital, Liverpool) The increasing demand for upper gastrointestinal endoscopy (UGE) suggests the need for priority allocation to ensure optimal use of the service. Scoring systems presently in use are based largely on symptoms. We investigated the value of UGE in 720 anaemic patients with no gastrointestinal symptoms (288 men, 432 women). A total of 350 (49%) had an ulcerative lesion. Of these, 77 (22%) were gastric ulcer, 73 (21%) severe oesophagitis, 66 (19%) severe gastritis or duodenitis, 63 (18%) carcinoma. 42 (12%) duodenal ulcer, and 17 (5%) gastric or duodenal polyps. Unsuspected coeliac disease was found in a further 10 patients, including four premenopausal women, two of whom had previously had a hysterectomy for recurrent anaemia. When analysed by age, the prevalence of disease increased greatly from 32% in patients less than 40 years to 60% in those over 70. While follow up does not yet allow coexisting silent colonic pathology to be completely
excluded, the diagnostic yield from UGE in the investigation of iron deficiency anaemia is high, especially in the elderly. Those with a negative examination, particularly younger women, should have duodenal biopsy examination to exclude coeliac disease.

Endoscopic palliation of malignant obstructive jaundice in Lothian

C RAIGOPAL, D C GRIEVE, AND K R PALMER (Gastro-intestinal Unit, Western General Hospital, Edinburgh) Between January 1987 and March 1989, 135 patients were referred to a single unit for endoscopic management of malignant obstructive jaundice. They underwent a total of 168 endoscopic and percutaneous procedures. Their age was, mean (SD), 71 (11) years; mean serum bilirubin concentration was 273 (120) μmol/l. Biopsy specimens were obtained from all subjects by percutaneous guided fine needle aspiration or Tru-cut, endoscopy or laparotomy.

Seventy eight patients had pancreatic cancer. In 14 (18%) duodenal invasion made endoscopic stenting impossible and gastroenterostomy with biliary bypass was performed; two patients died postoperatively. Fifty nine (92%) of the remaining patients eventually underwent successful insertion of a 10 or 12 F stent; this required a combined percutaneous and endoscopic approach in seven patients. Six subjects with apparently localised tumours underwent laparotomy with a view to a Whipples operation but resection was impossible in all. Ten patients had ampullary carcinomas and underwent surgical resection (six patients) or palliation by endoscopic sphincterotomy (four).

The remaining 47 patients had biliary obstruction due to other malignant diseases; cholangiocarcinoma (22 subjects), secondary tumours (eight), undetermined (17). Thirty five (81%) underwent successful stenting, requiring a combined approach in six cases. Patients with hilar obstruction posed the greatest challenge. Complications developed in 14% of patients, principally pancreatitis (5%), bleeding (6%), and cholangitis (3%). In addition internal stenting was impossible in five patients who were left with an external biliary drain. Hospital mortality was 9%.

With perseverance and ingenuity endoscopic palliation can safely be achieved in most patients presenting with malignant biliary obstruction.

Quick kit percutaneous endoscopic gastrostomy: an easy and reliable method of long term artificial enteral feeding

J CRAMPTON, R GREATEX, AND G NEALE (Department of Gastroenterology, Addenbrooke’s Hospital, Cambridge) Percutaneous endoscopic gastrostomy (PEG) has recently become an established technique for enteral feeding in patients with swallowing difficulties. Previous methods have relied upon the use of Malecot or other catheters, which, although effective, are cumbersome to insert and often cause discomfort. This report describes our experience with a quick kit PEG in 12 patients. The patients ranged between 14 and 86 years and the commonest indication for PEG feeding was neurological dysphagia due to cerebrovascular disease (n=6), motorneurone disease (n=3), degenerative neurological disease, (n=1) and trauma (n=1).

All procedures were performed with local anaesthetic and intravenous diazepam sedation and the procedure time averaged 10 minutes. Successful feeding gastrostomy was established in all cases including one patient with a Polya partial gastrectomy. Feeding was started within 24 hours. Complications included asymptomatic pneumoperitoneum and localised peritonitis, the latter settling with antibiotics alone. All patients were satisfied with the results up to 18 months. The case with which kit gastrostomy can be performed suggests that this technique deserves increasing use.

Screening young dyspeptic patients for Campylobacter pylori

G M SORALA, B J RATHBONE, A T R AXON, M F DIXON, R V HEATLEY, AND J W WATTS (Gastroenterology Unit and Dept of Pathology, General Infirmary, Leeds and Deps of Medicine and Pathology, St James’s University Hospital, Leeds) Endoscopic workloads are increasing and strategies to rationalise them are required. One suggestion has been endoscopic only those over 45 years, but this would fail to identify young patients with ulceration. Another strategy would be to endoscope only those young patients at high risk for peptic ulcer. Campylobacter pylori is a marker of duodenal ulceration, being found in >90% of cases, and can be detected non-invasively by serology with a predictive value 90%.

The potential diagnostic yields and savings of the two strategies were assessed using a model of 680 dyspepsia clinic patients in whom C pylori had been diagnosed histologically. A simple age restriction of 30 years would result in 22% fewer endoscopies, but 15% of all ulcers would be missed. With screening of those <30 years only 1.5% ulcers would be missed with 13% fewer investigations. Increasing the age limit to 50 years would result in 61% of endoscopies being saved but 55% ulcers missed. Screening of those <50 would result in only 4.4% ulcers being missed for 30% fewer endoscopies. The positive predictive value of presence of C pylori for ulceration was 31% in young dyspeptics.

Using C pylori as a marker could thus decrease the endoscopy load while still identifying young patients with ulcers.

Radially delivered Nd-YAG laser in the canine gastrointestinal tract and biliary tree

F N BRENAN, B H LAURENCE, J N SINCLAIR, AND P ROBBINS (Gastroenterology/Liver Unit, Deps of Pathology and Cardiology, Sir Charles Gairdner Hospital, Nedlands, Western Australia) The endoscopic use of Nd-YAG laser to palliate malignant gastrointestinal (GI) obstruction is well established. New laser delivery systems may overcome the problems of frequent, prolonged treatment sessions and may be more readily applied to the biliary tree. A 3 mm diameter balloon catheter incorporating a quartz fibre with diffusing tip (USCI Bard) developed for laser angioplasty enables laser energy to be applied over 360°. The results of applying this system in canine GI and biliary tracts is reported.

Anaesthetised mongrel dogs (14–20 kg) were used and laser was applied via the balloon to the mucosa of the oesophagus, stomach, and common bile duct (CBD). Nd-YAG laser (Quantatron 1500) of varying power (5–25 W) and pulse duration (1–30 s) was delivered and the tissue examined for gross and histologic effects. In the stomach, 0–5–2.0 cm grey zones of coagulation with marginal hyperaemia were observed; coagulative necrosis confirmed histologically – the size and depth of the lesion being proportional to total energy supplied. Less noticeable changes were seen in the oesophagus and higher energy levels were required to induce equivalent lesions. In the CBD, low energy levels produced deep lesions but changes were patchy, possibly related to the energy diffusing characteristics of the balloon. We conclude that radially delivered Nd-YAG laser will induce lesions of predictable depth in the canine stomach and oesophagus and
is likely to have safe application in obstructing GI malignancy in man.

**Peroperative enteroscopy in Peutz-Jeghers polyposis**

R K S Phillips, A D Spigelman, and J P S Thomson (St Mark’s Hospital and The Professorial Surgical Unit, St Bartholomew’s Hospital, London) Between 1943 and 1987, 23 Peutz-Jeghers patients (11 men, 12 women) underwent 56 laparotomies (one laparotomy=seven patients, two=six, three=six, four=two, five=one, and six=one) at several hospitals. In eight patients, 15 laparotomies were performed within two years of the preceding one. In an attempt to reduce the rate of repeat laparotomy, we have performed peroperative enteroscopy (peroral introduction of paediatric colonoscope (three), perenterotomy introduction of gastroscope (two)), in addition to conventional methods (palpation/transillumination) of polyp localisation in five patients (two men, three women, age range 4–21 y, mean 12). At operation, 28 polyps were found by palpation and transillumination in this group of patients. Intra-operative enteroscopy identified an additional 17 polyps. Polyps were removed by enterotomy (21), endoscopic snaring (18), or hot biopsy (six). Peroperative enteroscopy identified 38% of the total number of small bowel polyps, which would otherwise have been overlooked. In addition, 65% of these were of a sufficient size to warrant diathermy snare removal rather than hot biopsy.

The frequency of further laparotomy should be reduced by more detailed attention to the removal of all polyps.

**Effect of dydrogesterone on colonic motility and transit in women with premenstrual syndrome**

V Jones, D F Evans, G L Amont, R Watson, and M Macpherson (Depts of Surgery and Obstetrics and Gynaecology, University Hospital, Nottingham) Bloating, abdominal pain, and constipation are common manifestations of the premenstrual syndrome (PMS), possibly caused by alterations in colonic motility affected by circulating progesterone. Colonic motility and whole gut transit were measured in nine women with PMS before and during dydrogesterone (10 mg bd, administered for 16 days beginning on day 10 of the menstrual cycle. Motility was recorded for 24 hours using a pressure sensitive radiotelemetry capsule and portable equipment worn by the subject. Whole gut transit was measured with radio-opaque markers. A motility index (MI) was calculated for basal, postprandial, and night periods. The untreated values were compared with those of 11 control women.

Basal and postprandial MI were higher in the PMS group than in controls (median basal MI control 4.2, PMS 11.9; p 0.05); median postprandial MI control 6.8, PMS 15.6; p 0.05). During dydrogesterone treatment the postprandial MI was significantly reduced compared with the pretreatment values (median pretreatment MI 15.6, post-treatment MI 2.4; p 0.04). There was no difference in whole gut transit between control values or pre- and treatment PMS values. Colonic motility was significantly higher in patients with PMS than in controls and food stimulated motility was significantly reduced by dydrogesterone. Despite this measured difference there was no change in gut symptoms on treatment.

**A simple graphical method for comparing three measurements of whole gut transit time with the normal range using a single abdominal radiograph**

R C Evans, M A Kamm, J M Hinton, and J E Lennard-Jones (St Mark’s Hospital, London) A simple clinical method that minimises day to day variation is needed for measuring whether or not a patient’s whole gut transit time is within the normal range.

Twenty healthy women without bowel symptoms (age mean (range) 32 years (22–47) ingested three sets of 20 radiologically distinguishable PVC markers on three successive days. All stools were collected and x-rayed and the number of retained markers present at 12 hourly intervals was determined until all the markers had been passed (recovery 99.5%). The mean (2SD) of retained markers at each interval was then determined. This was performed twice, in the follicular and luteal phases, which were biochemically confirmed. Similar results were analysed for 25 men (age mean (range) 31 years (17–44)).

Mean transit rates in the two phases of the menstrual cycle were not significantly different and all the results for the women have been combined. A normal range for women and men has been expressed as the proportion of shapes remaining in the body at each time (mean (2SD)). The proportions of retained markers (mean (2SD)) for women and men respectively were: 24 hours (90% (46), 91% (32)), 48 hours (48% (70), 35% (75)), 72 hours (17% (47), 13% (40)), 96 hours (6% (22), 5% (24)), 120 hours (2% (10), 2% (20)). The normal range has been expressed on a standard form graphically. If a subject takes three different radio-opaque markers at 0, 24, and 48 hours and a single radiograph is taken at 120 hours, results at 72, 96, and 120 hours after ingestion can be plotted and compared with the normal range.

**Longterm imaging of the gastrointestinal tract using echo planar magnetic resonance imaging**

D F Evans, G Lamont, M K Stehling, RCoxon, RJ Ordioge, A Blamire, P Gibbs, PMansfield, and JS Hardcastle (Depts of Physics and Surgery, University Hospital, Nottingham) Fasting and fed motility patterns of the gastric antrum and proximal small intestine were measured in six healthy volunteers using the echo planar magnetic resonance imaging (MRI) technique MBEST. Data acquisition times of 128 ms allowed imaging of the upper gastrointestinal (GI) tract in real time without image degradation or blurring. Subjects were imaged supine for two hours in order to study the fasting migrating motor complex (MMC) and the effect of food on this. Subjects were given 1 l tap water before imaging, this acted as a neutral non-toxic contrast medium to outline the gut lumen. The three phases of the MMC were observed in all subjects. This included, in some cases, the active phase (III), where a frequency of peristalsis of three per minute in the gastric antrum and 13 per minute in the duodenal bulb were counted. After food, fasting activity was replaced by the fed pattern as observed in manometric studies. The meal, easily distinguishable from the water, because of the different density of particles, was seen to slowly empty from the stomach.

The potential for quantitative measurements of the GI tract with this new imaging technique is an exciting development and will allow the measurement of transit and correlation with motility.

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D Kumar, E E Soffer, MJ Benson, and DL Wingate (Gastrointestinal Science Research
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Unit, London Hospital Medical College, London) Chronic abdominal pain of unknown origin is often referred to as 'functional abdominal pain' (FAP), and is characterised by multiple referrals and repeated negative investigations. We performed diagnostic manometry of the upper gut for 24–48 hours in 23 patients with FAP: all had chronic (>one year), unremitting, diffuse abdominal pain which was unresponsive to any treatment. None fitted the diagnostic criteria of irritable bowel syndrome (IBS). Motor activity was recorded from two to three strain gauge transducers spaced 15 cm apart in a nasojugal probe. All patients were freely ambulant and were allowed home during the study. Sixteen of the FAP patients exhibited one or more of several manometric abnormalities. Most had six to seven migrating motor complexes (MMCs) per 24 hours, but in three of 16, only two to three MMCs were seen. In four of 16, phase III episodes were simultaneous in all channels. Variable propagation velocity of single or successive MMCs along the study segment, or of successive MMCs was seen in six of 16. In two of 16, abnormal contraction frequencies were seen during phase III activity and, in two of 16, tachyarrhythmias (18–23 contractions per min) occurred. In three of 16, there was no change in motor pattern on feeding. In seven of 16, clustered contractions were seen for periods of one to 14 hours during sleep. These motor abnormalities resemble those found in intestinal pseudo-obstruction. These patients had no signs of obstruction, however, nor was their pain associated with motor events; thus a visceral sensory neuropathy is suspected.

Motility effects of electrical stimulation of the parasympathetic supply to the left colon and anorectum in man

N R Binnie, A N Smith, P Edmond, and G Creasey (University Dept of Surgery, Western General Hospital, Edinburgh and Spinal Injuries Centre, Edenhall Hospital, Musselburgh, Midlothian) The colonic and anorectal motility responses to S2, 3, and 4 nerve root stimulation of the pelvic parasympathetic nerves was studied in seven paraplegic subjects with implanted Brindley electrodes for the control of micturition. Stimulation of the S2, 3, and 4 nerve roots sequentially increased wave heights from the transverse colon distally. The mean motility response (motility indices) was greatest in the splenic flexure (splenic flexure – transverse colon or sigmoid colon p<0.01).

After individual nerve roots' stimulation, S3 activation produced the greatest effect for both wave heights and motility index (splenic flexure – transverse colon p<0.01; splenic flexure – sigmoid colon p<0.05). S2 produced the least response. S4 caused effects on the rectum (rectum – sigmoid colon p<0.01), partly as an effect on the striated muscle of the pelvic floor since anal canal pressures rose to values above the physiological range simultaneously with 'acute' radiological changes in the anorectal angle. These effects on the pelvic floor may promote continence but the pressure gradient induced by the contractions of the smooth muscle of the left colon should also promote emptying if they outlast the rapidly declining striated muscle pelvic floor contractions.

Relation between stool form on a seven point scale and symptoms of urgency, straining, and incomplete evacuation: a new way of looking at irritable bowel syndrome

K W Heaton and S Ghosh (University Dept of Medicine, Bristol Royal Infirmary, Bristol) Stool form classified according to a 1–7 point scale correlates with intestinal transit time but the clinical value of this scale has not been shown.

Fifty three women with irritable bowel syndrome (IBS) (26 hospital patients and 27 uncompaining sufferers or non-patients detected by population screening) and 27 healthy controls kept defecation diaries for 31 days, noting stool form, urgency, straining, and incomplete evacuation.

In controls urgency occurred with 100% of form 7 (watery) stools but no form 1 stools (scybala). Conversely straining occurred with no form 7 stools but 68% form 1. With forms 2 to 6 there was, stepwise, increasing urgency and decreasing straining (p<0.001). In contrast, incomplete evacuation had a U-shaped relation to stool form; the minimum being at form 4 (long, soft, smooth). Prevalence values were: form 1, 43%; form 2, 23%; form 3, 7%; form 4, 5%; form 5, 17% form 6, 35%; and form 7, 71%. As form 4 also incurred little urgency or straining it seems the 'ideal stool'.

In IBS patients these relations were distorted or lost, all symptoms being common with all stool forms; incomplete evacuation was equally prevalent (50–70%) across the scale.

The findings in non-patients resembled controls.

We conclude that stool form and defecatory symptoms are closely related in the general population but not in IBS patients. In IBS, rectal sensations are often inappropriate to rectal contents.

Effect of diabetic autonomic neuropathy on the internal anal sphincter

M G O Riordan, T Crofty, D J O'Sullivan, and W O Kirwan (University Dept of Surgery and Medicine, Regional Hospital, Cork, Ireland) Recent studies have shown significantly reduced resting anal canal pressures in diabetics with diarrhea and incontinence, but no reduction in asymptomatic patients has been shown. It is not known, however, whether asymptomatic diabetics with autonomic neuropathy have a reduced resting anal pressure, or whether neuropathy affects the rectoanal inhibitory reflex.

Eighteen patients (nine men and nine women) with longstanding diabetes mellitus (duration, mean range) (17 (10–37) years, were studied. They were aged 61 (20–73) years. Autonomic neuropathy was graded as absent, early, definite, or severe using five standard cardiovascular autonomic function tests (as described by Ewing and Clarke). Anal canal pressures were measured using a catheter tipped microtransducer. Rectoanal inhibitory reflex was assessed after inflation of 20, 40, 60, 80, and 100 ml of air.

Four of the 16 asymptomatic diabetics had no evidence of autonomic neuropathy, four had early, two definite, and six severe neuropathy. There was no difference in resting pressure between those without neuropathy (mean 68 mmHg) and those with early neuropathy (mean 85 mmHg), but there was a significantly lower resting pressure in those with definite or severe neuropathy (mean 39 mmHg) than in either of the other groups (p<0.01). Both of the two patients with diarrhea had evidence of severe neuropathy, and their resting pressures were 30 and 41 mmHg respectively. The rectoanal inhibitory reflex was present in all patients, and the amplitude (% drop), threshold, or duration of the reflex were unrelated to the degree of autonomic neuropathy.

This subclinical abnormality in resting anal sphincter tone in patients with established diabetic autonomic neuropathy may well represent an early stage in the
development of diabetic diarrhoea and incontinence.

Is improvement of continence after recto-

G S Duthie and D C C Bartolo (University

Abdominal rectectomy for rectal prolapse re-"serves continence in approxi-

To determine if either factor has a signifi-

All vaginal deliveries increased anal sen-

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Two patients underwent IAS strip myectomy.

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Comparison of mesalazine with sulphasa-
zine in prophylactic treatment of ulcera-
tive colitis

G B PORRO, S ARIZZONE, R FASULI, M
PETRILLO, AND S DESIDERI (Dept of Gastro-
enterology and Endoscopy, L. Sacco Hospital,
Milan, Italy) Different oral preparations of 5-ASA have been reported to be as effective as sulphasalazine (SASP) in prolonging remission in ulcerative colitis (UC).

We compared, in a double blind trial, a new formulation of mesalazine (Claversal, SKF) (500 mg bd) with SASP (1 g bd), in 60 patients (32 men and 28 women; age, mean (range) 32 (18-61) years, with quiescent UC but at least one relapse in the previous 12 months. The end point was considered a relapse requiring systemic corticosteroids in the course of a one year period of observation.

The two groups were comparable with regard to all pre-trial characteristics.

No significant difference was observed in the relapse rate in the two groups either after six months (30% SKF, 33% SASP) or after 12 months (50% SKF, 53% SASP). Diarrhea was reported in 14% of the SKF group and 12% of the SASP group (NS).

We conclude that: (1) SKF was at least as effective as SASP in maintaining remission in UC; (2) the relapse rate was, however, higher than expected in both groups; (3) the incidence of side effects was similar with the two treatments.

Antineutrophil cytoplasmic antibodies in inflammatory bowel disease

J JACKSON, C KELLY, D G WEIR, AND C
FEIGHERY (Dept of Immunology and
Medicine, St James Hospital, Dublin,
Ireland) Antineutrophil cytoplasmic antibo-
dies (ANCA) have been reported in associa-
tion with various forms of vasculitis and
systemic lupus erythematosus. In this study the incidence of ANCA in inflammatory bowel disease was examined. Using an indirect immunofluorescence technique, coded sera from 16 patients with ulcerative colitis, 13 patients with Crohn’s disease, 10 patients with sarcoidosis, 74 patients with connective tissue disorders, and 31 normal subjects were examined for the presence of ANCA. Positive results were found in 18% of patients with ulcerative colitis, 61% with Crohn’s disease, 50% with sarcoidosis, 24% with connective tissue disease, and 0% of normal controls. Most patients with connective tissue disease gave perinuclear pattern of fluorescence while most with inflammatory bowel disease and sarcoidosis gave a cytoplasmic pattern of fluorescence.

The association of these antibodies with Crohn’s disease, sarcoidosis, and Wegener’s granulomatosis suggest a strong association between these antibodies and granuloma formation. This finding together with the known association between granulomata and neutrophil defects (chronic granulomatous disease) suggest a possible role for aberrant neutrophil function in the pathogenesis of disorders characterised by the presence of granuloma.

Do patients with fresh rectal bleeding, haemorrhoids, and a normal rigid sigmoido-
scopy require further investigation?

G J LAMONT, W M THOMAS, G PYE, AND D L
MORRIS (Dept of Surgery, University
Hospital, Nottingham) Patients with bright red rectal bleeding suggestive of haemor-
hroids are not usually subjected to investiga-
tion other than proctoscopy and rigid sigmoidoscopy. We have investigated patients presenting with bright red rectal bleeding, obvious haemorrhoids, and a normal rigid sigmoidoscopic examination by 60 cm fibreoptic flexible sigmoidoscopy.

A total of 141 patients were entered into the study between January 1988 and May 1989. There was a male preponderance (87 men; 54 women); age median (range) was 51-4 years (20-81). No cancers were detected. Although 10 patients (7.1%) were found to have an adenomatous polypl, each of which was bigger than 1 cm. All polyps were more than 25 cm from the anal verge and were removed at subsequent colono-
scopy. When stratified by age, the results were as follows:

(1) <50 years old (n=60); three adenomatous polyps in three patients (5-0%); (2) >50 years old (n=81); eight adenomatous polyps in seven patients (8-6%).

Although there is no evidence to suggest that the polyps were responsible for the bleeding, this high incidence of adenomas suggests that further investigation is warranted in patients with symptoms solely suggestive of haemorrhoids.

Role of cell free cytotoxicity in patients undergoing intraarterial interleukin-2 therapy for gastrointestinal cancer

P DURDEY, M TURKISH, D H JOHNSTON, M F
GRAHN, P ALLEN, M G MACEY, AND N S
WILLIAMS (Surgical Unit, The London
Hospital, London) Interleukin-2 (IL-2) therapy for malignancy is believed to be based on enhancement of cell mediated immunity. Humoral factors could also be implicated. We have measured the effect of cell-free peripheral blood serum from five patients undergoing intraarterial IL-2 therapy for disseminated abdominal malignancy, on growth in vitro of multicellular tumour spheroids (MTS) derived from the HT29 human colorectal cell line (eight for each experiment). Serum taken during treatment cycles caused significant growth retardation when compared with serum from seven healthy volunteers. Relative volume increases (RVI) over five days

Role of upper gastrointestinal investigation in a fecal occult blood screening study for colorectal neoplasia

W M THOMAS AND J D HARDCASTLE (Dept of
Surgery, University Hospital, Nottingham)
After faecal occult blood (FOB) screening, patients with positive tests may be shown to be free of colorectal neoplasia – should these people undergo upper gastrointestinal investigation?

A total of 16985 randomly selected people (50-74 years) completed FOB tests. Some 447 (2.6%) were positive and underwent bowel investigations. No neoplastic disease was identified in 284 (63%) of these. Fourteen (5%) also underwent gastroscopy for upper gastrointestinal (GI) symptoms: benign conditions were identified in five and gastric cancer in one. No further investigations were instituted in the remaining 269 subjects who have now been followed up for a period of median (range 5 (2-8) years. Five have been referred for benign upper GI conditions, none for upper GI malignancy.

Thirty one subjects have died – one of gastric carcinoma (a patient who had undergone a previous partial gastrectomy for DU and who had persistent upper GI symptoms). The remaining deaths were unrelated to the upper GI tract.

Nineteen people who have left the trial area have been monitored for the development of malignant disease; none have presented with GI malignancy.

The data suggest the opinion that upper GI investigations need not be performed routinely in this group of individuals, but should be reserved for those with relevant symptoms.
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A host cytotoxic reaction to colonic carcinoma

R I SWIFT, C WORMAN, N A HABIR, M J HERSHMAN, C B WOOD (Dept of Surgery, Royal Postgraduate Medical School and Dept of Haematology, University College Hospital, London) The presence of a leucocyte infiltrate into colonic neoplasms is thought to be mainly an inflammatory response, but may also represent a host immune reaction. We have looked for the presence of cytotoxic T lymphocytes in colorectal cancer tissue compared with normal colon.

The mechanism of T cell cytotoxicity has recently received much interest with the discovery of a group of enzymes that share an important role in the cytotoxic mechanism. We have used a newly developed stain that identified serine esterases within the intracellular granules of cytotoxic cells. Monoclonal antibody stains for CD4 and CD8 subsets of T cells have been used to characterise the lymphocyte population present in tumour tissue. Twenty samples of colon tissue were used, 10 benign and 10 malignant. The results clearly show that malignant tissue has a significantly greater infiltration by cytotoxic T cells than benign tissue (p<0.001 Mann Whitney U Test).

In conclusion, we have shown that a serine esterase stain acts as a specific marker for cytotoxic cells, and this can be used to show a significant host T cell cytotoxic response to the presence of malignant tissue.

Nucleolar organiser regions and ploidy values predict biological behaviour of colorectal tumours

K MORAN, J COOKE, G FORSTER, S SHEEHAN, P DERVAN, T GOREY, AND J M FITZPATRICK (J CROWE) (Mater Misericordiae Hospital and University College, Dublin and Royal Liverpool Hospital) Dukes' classification and histological differentiation fail to predict outcome in advanced colorectal cancer. Nuclear organiser region counts (NORs) reflect cellular activity, and ploidy status can reflect tumour differentiation and behaviour. We studied the prognostic value of NORs and ploidy status and their correlation with established prognostic indices and the biological differences between primary tumours (1ª and lymph node metastases (LN) in advanced colorectal cancer.

Fifty one patients aged, median (range) 61-6 (35-81) years with Dukes' C tumours were studied. All were followed for a minimum of five years. Sections from 1ª and LN were stained for NORs in all 51 patients, and ploidy status was determined by flow cytometry in 40. The NORs and ploidy status were correlated with age, sex, histological differentiation, presence of liver metastases, and survival time, and the independent significance of individual variables was determined using Cox's multivariate regression analysis.

Sixteen patients survived five years. Survivors had lower NORs than non-survivors (p<0.05) and NORs were the most important individual variable in predicting survival (p<0.01). An upgrade in ploidy status was noted with 12 aneuploid 1ª having diploid LN while no diploid 1ª regressed. Survivors had significantly less aneuploid metastases χ²=4.21, p<0.05, and patients with diploid LN had longer median survival times (38-2 months) than patients with aneuploid LN (14-2 months, p<0.05).

The NOR scores were more accurate than conventional prognostic indices. A selective proliferation of diploid cells occurs during metastases. This may explain the insensitivity of carcinomobryonogenic antigen values, which are associated with aneuploidy, and has important implications for our understanding of tumour kinetics and the development of systemic therapy.

Effect of long acting somatostatin on the cancer cell kinetic index in vivo in human primary rectal carcinoma

S Y IFITIKHAR, S A WATSON, AND D L MORRIS (Dept of Surgery, University Hospital, Nottingham and Cancer Research Campaign Laboratories, Nottingham University, Nottingham) The long acting somatostatin analogue, SMS 201.995, has been shown to inhibit some gastrointestinal cancer cells in vitro and in vivo. The aim of this study was to evaluate the effect of subcutaneously administered SMS 201.995 on the kinetic index of the cancer cells from 15 patients with primary rectal carcinoma. The index was measured using Ki67, a mouse monoclonal antibody recognising an antigen expressed by cells in proliferative phase of growth.

Nine patients were given SMS 201.995; administered subcutaneously by continuous infusion at a dose of 600 µg/h for 14 days. Each patient acted as his own control and a further six untreated patients were studied. Biopsy specimens for kinetic index were taken at the beginning and end of the SMS treatment. The mean linear fluorescence/cell and percentage positively staining cells were measured by flow cytometry. Four of eight SMS-treated patients showed a decrease of 99%, 95-4%, 60%, and 98% in Ki67 percentage positive cells; three treated patients showed increases of 36-3%, 19-5%, 300%, and one had no change. All six untreated patients showed an increase of 28%, 27%, 32%, 200%, 20%, and 21%.

We conclude that SMS 201.995 reduces Ki67 (mitotic index) in vivo in some patients with rectal carcinoma. This is an original and potentially clinically important finding.

Prognostic significance of lymphocytic infiltration and collagen IV expression in colorectal carcinoma

J A BRUIN, G J A OFFERHAUS, E MOLYVA, I H STIJNEN, C H M VAN ONSARUGGE-BONDON, J B M J JANSEN, C B W LAMERS PH J HOEDEMAKER, AND G J FLEUREN (Depts of Pathology and Gastroenterology, University Hospital, Leiden, The Netherlands) Dukes' classification is well established as a prognostic factor in colorectal cancer patients. Within each Dukes' class, however, the prognosis of subsets of patients may vary considerably. Recent studies have pointed towards a prognostic significance of genetic events in colorectal carcinoma. Techniques for assessing these events require tissue samples with relatively high loads of neoplastic cells without too much surrounding inflammation cells or tumour stroma. Thus, selection bias may limit the interpretation of the results. This is especially important because it has been suggested that inflammatory cells and deposition of basement membrane components may have prognostic value per se.

To assess the influence of lymphocytic infiltration and expression of collagen IV on
the prognosis of colorectal cancer patients, a longitudinal study of 154 patients with colorectal cancer operated upon between 1967 and 1974 was performed. Follow up was at least 15 years. Lymphocytic infiltration and collagen IV expression were scored as mild, moderate, or severe. In addition, age, sex, Dukes' classification, grade of tumour differentiation, vaso-invasion, and number of positive lymph nodes were also scored and analysed as independent variables. Survival was analysed by a Cox proportional hazards model.

The density of lymphocytic infiltration showed no significant influence on mortality. Expression of collagen IV was not of influence on the prognosis when analysed together with the Dukes' classification (p=0.16). When analysed as a single variable, however, expression of collagen IV was significantly (p<0.05) related to a better prognosis.

We therefore conclude that expression of basement membrane components like collagen IV in tumour stroma has prognostic value per se. This must be taken into account when studying these tumours.

Tissue procoagulant activity may be important in sustaining metastatic growth

N CARY, J L FRANCIS, M LOZIDOU, A COOPER, AND I TAYLOR (University Surgical Unit and Dept of Haematology, General Hospital, Southampton) Given a similar tumour burden, not all tissues are similarly receptive to metastases. Trauma and regeneration are known promoting factors and a link between tissue procoagulant activity and tumour growth has been suggested. We have measured factor X-activating activity (FXAA) in (1) various rat tissues, (2) anastomosed and normal rat bowel, (3) rat liver regenerating after partial hepatectomy, and (4) various rat organs after oral anticoagulation. The results were correlated with the ability to sustain metastatic growth.

FXAA was significantly (p<0.001) higher in adrenal (median (interquartile range) 13-7 (8-5-25.3) and lung (7-7, 6-3-12-3), organs frequently the site of metastasis, than liver (0-9, 0-3-3-7) or colon (0-4, 0-2-0-8). FXAA was significantly (p<0.05) reduced by warfarin (eg median adrenal activity reduced from 13-7 to 1-3). After colonic anastomosis, FXAA peaked at three to five days (ratio anastomosed:non-anastomosed colon = 3:5:1). After partial hepatectomy a similar peak was observed (hepatectomy:prehepatectomy liver = 4:1). These peaks coincide with the maximal take of metastases after intra-arterial and intra-portal injection of tumour cells.

These studies show a broad correlation between the FXAA of tissues and their predilection for tumour growth. Warfarin, which reduces metastases in several models, also reduces tissue FXAA. The ability to activate factor X may therefore influence the development and growth of metastases in the liver and around colonic anastomoses.

Influence of tumour cell antigen expression on recurrence in patients with colorectal cancer

N CARMARGE, J G DURRANT, K C BAILLANTYNE, P CLARKE, AND J D HARDCASTLE (Depts of Surgery and Cancer Research, University of Nottingham) Intertumour variation in tumour associated antigen expression is frequent in colorectal cancer, and we have previously shown that tumour cells which express carcinoembryonic antigen have a higher proportion of DNA abnormalities (aneuploidy). We studied tumour cell antigen expression prospectively in patients with colorectal cancer to assess the relation to recurrence at a minimum follow up of mean (range) 12 months (12-62).

Tumour associated antigens were measured by flow cytometry in tumour cells from fresh colorectal cancers, using monoclonal antibodies anti-CEA, 791T/36 (osteosacoma antibody), and C14 (anti-adenoma antibody).

In patients without metastases, those with high expression of CEA (>500 fl, U/cell) have a greater recurrence rate (20 of 46 (44%)) than those with low expression (21 of 69 (30%)) (Stat=3-7, p=0-05). Patients with high expression of 791T/36 antigen (>30 fl, U/cell) also have more recurrences (30 of 73 (40%)) compared with low expression (six of 27 (22%)) (Stat=3-7, p=0-05). This difference in recurrence seemed mainly for aneuploid tumours. Expression of adenoma antibody, however, had no influence on recurrence.

Tumour cell antigen expression seems to identify phenotypes which have a higher risk of tumour recurrence, but potentially more targets for antibody directed treatment.

Effect of epidermal growth factor on colonic epithelial growth and its relation to experimental carcinogenesis

J REEVES, R C RICHARDS, AND J COOKE (University Dept of Surgery, Royal Liverpool Hospital and Dept of Human Anatomy and Cell Biology, University of Liverpool, Liverpool) Although intraluminal epidermal growth factor (EGF) is known to stimulate cell proliferation in the upper gastrointestinal tract, its role in the large bowel has not been established. We have therefore studied the effect of intraluminal EGF on both normal growth and carcinogenesis in the rat colon.

Colonie cancer was induced in rats by azoxymethane (10 mg/kg/week for 12 weeks). A control group of animals were similarly dosed with isotonic saline. In each group, animals were randomised to receive EGF (5 ng or 75 ng/ml) in a volume of 0.5 ml or the same volume of saline via a rectal tube daily for 23 weeks. At this time, crypt cell proliferation rates (CCPR) were determined by thymidine techniques at 5 and 10 cm from the anus. Irrigation with radiolabelled EGF showed activity to 10 cm.

The CCPR in control animals receiving rectal saline or 5 ng/ml EGF were similar at both sites. 75 ng/ml EGF significantly increased (p<0.05, Student's t test) the CCPR at 5 cm (mean (SD) 8.29 (9.82)) compared with animals receiving saline (5.31 (6.1)) and 5 ng/ml EGF (4.45 (5.54)). Azoxymethane increased the CCPR at 5 cm in the colon of animals receiving saline (10.99 (9.81)) and 5 ng/ml EGF (9.92 (1.73)). The higher dose of EGF (75 ng/ml), however, significantly suppressed the CCPR at 5 cm (4.39 (1.37), p<0.05).

These results suggest that: (1) luminal EGF and azoxymethane independently increase colonic CCPR, but that their effects are not synergistic; (2) EGF may have a role in normal epithelial growth but does not potentiate carcinogenesis.

Epithelial cell proliferation in remaining colorectal mucosa after surgery for cancer of the large bowel

M POZZ DE LEON, L RONCucci, A SCALMATI, AND G GHIDINI (Istituto di Patologia Medica e Divisione di Chirurgia d'Urgenza, Università di Modena, Modena, Italy) It has been suggested that the frequency of multiple colorectal tumours may reflect an abnormal pattern of cell kinetics in the remaining mucosa after surgery. We set out to evaluate the effect of segmental resection (for colorectal cancer) on cell replication in the large bowel mucosa.

Specimens of mucosa were taken from 11 patients undergoing colonoscopy six to 24 months after colonic resection and from 23 controls, and were processed with standard
autoradiographic techniques. Longitudinal hemicyrpt were divided into five equal compartments – from the base (compartment 1) to the surface (compartment 5). Total and labelled cells were counted. The labelling index (LI) was the ratio of labelled to total (%). Total LI and LI per compartment were similar in patients and in controls. Both total and upper compartment LI, however, were significantly (p<0.01) higher in patients who showed recurrence of polyps than in those with a negative endoscopy.

We conclude that after resection colonic epithelial cell proliferation tends to become similar to that of controls. But in the subgroup of patients in whom polyps recur, changes in cell kinetics are usually observed. Therefore, the evaluation of cell proliferation in the follow-up of patients who have undergone surgery may be useful in identifying those at major risk for multiple tumours.

Does irradiation with cancerridial agent reduce local recurrence rate after resection for colonic carcinoma?

P I CULLEN, V KOMBOROS, AND P B BOULOS (Dept of Surgery, University College London, Rayne Institute, London) Irradiation of the bowel stumps with cancerridial agents before anastomosis has been recommended for preventing local recurrence due to implantation of exfoliated cancer cells at the resection margins. This approach, however, has not been adequately evaluated clinically and is investigated in this study.

One hundred and twenty-five consecutive patients who received either intraluminal mercuric perchloride 0-5% (group I: n=64), or no cancerridial agent (group II: n=61), while undergoing restorative resection for sigmoid and rectal carcinoma were studied. The groups were well matched for age mean (SD) (group I 67.9 (9.2), group II 62.3 (12.9)), sex (I: 27 men, 37 women; II: 31 men, 30 women), tumour level (I: sigmoid 36, rectum 28; II: 32 sigmoid, 29 rectum), and stage (A=13 v 9, p>0.5; B=27 v 25, p>0.5; C=24 v 27, p=0.5). Differences were detected in histological grading with more well differentiated tumours in group II. 23 v 9, p<0.01, and more moderately differentiated tumours in group I 50 v 35, p<0.001. There was no difference in the complication rate (I: 40-6% v II: 45-9%) or postoperative mortality (I: 6-25% v II: 4-91%). The mean (SD) follow up time was similar (33 6 (28 7) months v 50 9 (57 4)), with six local recurrences detected in group I and 11 in group II. p<0.02. The mean (SD) time to recurrence in group I was 12.8 (7 9) months v 23 2 (14 8) in group II. p<0.001.

These results clearly show an effective benefit with mercuric perchloride irradiation in reducing local recurrences – which, interestingly, presented earlier in this study.

Hartmann's reversal – when and how?

N PEARCE AND S J KARRAN (University Surgical Unit, Southampton General Hospital, Southampton) The dangers associated with 'reversal' of Hartmann's operation (emergency sigmoid resection with end colostomy and rectal preservation) have not previously been reported. We have reviewed the last 145 patients undergoing Hartmann's procedure in Southampton, in 80 of whom reanastomosis was undertaken (diverticulitis 57, carcinoma 19, and miscellaneous four), with particular reference to major anastomotic complications.

In the 40 patients reanastomosed within six months of the original procedure, there were 15 major anastomotic complications (13 fistulae/leaks, one stricture, one haemorrhage) compared with three (two strictures (one requiring permanent colostomy), one haemorrhage) in the 40 patients reanastomosed later than six months (p<0.001) Fisher's test). All late complications, all strictures, and all colovaginal fistulae (three) followed anastomoses with the EAA staple 'gun'. Of the 13 patients with early fistulae/leaks, four developed septicaemia, nine required permanent colostomy, and three died. When reanastomosis was attempted before three months six of 12 patients developed fistulae (50%), compared with seven of 28 (25%) in whom the procedure was undertaken between three and six months. Mean hospital stay in the very early (under three months) group was 39 days, compared with 17 days in the three to six months group and 12 days in the delayed group (p<0.001, pcr and post six months). Overall morbidity was not affected by surgeon's grade, the method of reversal, or the initial pathology, though individual variations occurred.

Delayed (ie >six months) reanastomosis after Hartmann's operation is associated with an appreciably lower incidence of major anastomotic complications and a shorter hospital stay independent of other variables.

Treatment of diversion colitis with short chain fatty acids irradiation: a prospective study

F GUILLAUMOT, C NEUT, J F COLOMBEL, N VERPLANCKE, M LECOMTE, C RONDON, J C PARIS, AND A CORTII (CHU, 39037 Lille Cedex, France) A diminished production of short chain fatty acids (SCFA) because of an altered intestinal flora has been suggested in the pathogenesis of diversion colitis (DC). The aims of this study were: (1) to evaluate prospectively SCFA irradiation in DC; and (2) to compare the microbial flora in DC before and after SCFA irradiation.

A total of 13 patients with DC (inflammatory bowel disease, four; cancer, two; miscellaneous, seven) were studied. There were eight men and five women with a mean age of 48 years. Patients were given either a 60 ml enema containing SCFA (acetate: 60 mmol/l, propionate: 30, butyrate: 40) given either (group 1 n=6), or isotonic NaCl (group 2: n=seven) double blind twice a day for 14 days. Biopsy specimens were taken and bacteriological analyses were performed on days one and 14.

On day 14, endoscopic and histologic findings were similar to those on day 1 in both groups. Anaerobic and aerobic bacteria were reduced on day 14 v day 1 in both groups.

Endoscopic and histologic findings in DC were not improved by 14 days SCFA irradiation. The reduction in bacterial counts after SCFA and NaCl was probably due to an enema induced dilution. Other factors such as bacterial imbalance could play a part in the pathogenesis of DC.

Quality of life after restorative proctocolectomy for ulcerative colitis: an intact anal sphincter is preferable to mucosal proctectomy

P MSAGER, P J HOLDSWORTH, AND D JOHNSTON (University Dept of Surgery, General Infirmary, Leeds) Restorative proctocolectomy with a pelvic ileal reservoir (RP) is usually accompanied by mucosal proctectomy (MP) with an endo-anal anastomosis (MP+EEA). Our hypothesis was that avoidance of MP and preservation of the entire anal canal, with an end to end anastomosis (EEA) would be quicker, simpler, and yield better results with improved quality of life. We have shown previously that anal pressures and sensitivity were closer to the normal after EEA than after MP+EEA.

A detailed questionnaire and the Hospital Anxiety and Depression (HAD) test were administered to a consecutive series of 74 patients, each of whom had undergone successful RP more than one...
obtained from convalescent p<0.05; and both nation and foods, HAD found. stripping mucosal a line. Some 54% of the whom had evidence of vascular depression, specific foods, interference with lifestyle, and HAD depression scores.

When the entire anal canal is left intact, the reservoir being stapled to the anus and mucosal stripping avoided, the patients’ convalescence is smoother and their quality of life is better.

**Does rectal mucosa remain after stapled end to end pouch-anal anastomosis in ulcerative colitis?**

**P M Sagar, P J Holdsworth, P Quirke, M F Dixon, and D Johnston (University Dept of Surgery and Pathology, General Infirmary, Leeds)** It has been suggested that the functional results of restorative proctocolectomy with pelvic ileal reservoir (RP) might be improved by construction of the pouch-anal anastomosis end to end at the top of the anal canal, preserving the entire mucosa of the anal canal. It is difficult, however, to judge precisely the level of the anastomosis when using stapling instruments. Our hypothesis was that with this technique a fringe of rectal mucosa might remain and constitute a potential focus for continuing colitis and perhaps even carcinoma.

RP with stapled ileo-anal anastomosis (IAA) was performed in 42 patients, 19 of whom had an S reservoir and 23 a W reservoir. Target biopsy specimens taken 1 cm, 2 cm, and 4 cm above the dentate line were examined histologically for mucosal type, evidence of colitis, and the presence of dysplasia (median range) 14 months (3–43) after operation.

Transitional or squamous epithelium was identified in 20 out of 42 patients (48%). Rectal mucosa was present in 10 (24%) at 1 cm and 13 (31%) at 2 cm above the dentate line. Some 54% of the biopsy specimens which showed rectal mucosa had features of continuing, albeit mild, colitis, but no evidence of dysplasia or neoplasia was found. RP with stapled IAA was found to leave a small (1–2 cm) cuff of rectal tissue distal to the anastomosis in 31% of patients. No evidence was found that the clinical results were impaired in these patients.

**Can the incidence of pouch failure be reduced in restorative proctocolectomy?**

**P M Sagar, P J Holdsworth, and D Johnston (University Dept of Surgery, General Infirmary, Leeds)** Restorative proctocolectomy with a pelvic ileal reservoir (RP) is now widely used in the surgical treatment of ulcerative colitis and familial adenomatous polyposis. RP is associated with a relatively high morbidity, however, a prolonged convalescence, and eventual failure in 5–15% of patients. A consecutive series of 109 patients who underwent RP between 1980 and 1989 was studied to try to identify factors that may predispose to failure.

Mucosal proctectomy with endo-anal anastomosis was performed in 56 patients, and conservative proctocolectomy with preservation of the entire anal canal (without mucosectomy) in 53. The pouch design was duplicated (J) in 24, tripled (S) in 58, and quadrupled (W) in 27. Follow up was median (range) 42 months (4–106). The operation failed and the pouch had to be removed in 15 patients. Mucosectomy*, particularly with long rectal cuff*, pelvic sepsis†, and anastomatic dehiscence‡, significantly increased the risk of subsequent failure, whereas the design of the pouch, anastomotic stricture, pouchitis, and previous colectomy did not. Thus avoidance of mucosal stripping coupled with efforts to minimise pelvic sepsis should reduce the incidence of failure.

*p<0.01, †p<0.001.

**Functional bowel disorders: further indications for restorative proctocolectomy**

**K H overs, W K Miot, and M R B Keighley (Dept of Surgery, Queen Elizabeth Hospital, Birmingham)** Restorative proctocolectomy and ileoanal anastomosis is now well established as an alternative to panproctocolectomy and end ileostomy in patients with severe ulcerative colitis and familial adenomatous polyposis. Two cases of pouch formation have been reported after an unsuccessful ileoanal anastomosis for severe idiopathic constipation.

We report our experience of restorative proctocolectomy and ileo-anal anastomosis in 11 patients with functional bowel disorders. Seven were for idiopathic constipation after a failed subtotal colectomy and ileorectal anastomosis and four were as a primary procedure in patients with constipation and overflow incontinence associated with megarectum and megacolon. In all patients the alternative was a permanent stoma. With the exception of one patient whose pouch was eventually excised at their request, all of the remaining patients have had a satisfactory outcome. Stapled ileoanal anastomosis is rarely possible in megarectum and there is a high incidence of anastomosis leaks in this group. Nevertheless the longterm results have been good.

We suggest that two further indications for ileal pouch formation are selected patients with severe constipation who have had an unsuccessful ileorectal anastomosis and those who have megarectum associated with megacolon.

**Pouchitis after restorative proctocolectomy is associated with mucosal ischaemia**

**K H overs, M Sachaguchi, R Tudor, D Gourewich, W Miot, and M R B Keighley (Dept of Surgery, Queen Elizabeth Hospital, Edgbaston, Birmingham)** ‘Pouchitis’ has been reported to occur in 7–44% of patients after restorative proctocolectomy. This is a syndrome characterised by painful diarrhoea and urgency, associated with bleeding and ulceration on sigmoidoscopy, and a neutrophil infiltrate on ileal biopsy examination.

As the formation of a pouch sometimes involves vascular mobilisation of the small bowel we have assessed the mucosal blood flow of the pouch using laser doppler flowmetry.

The endoscopic probe (PF 309) of a perimed P2B laser doppler was passed down the biopsy channel of a colonoscope. Using a 12 kHz bandwidth, multiple flux readings were obtained from the pouch (n=23) and from ileostomy controls (n=12). Flux in the pouch mean (range) 0.89 v (0.18–1.8) was significantly lower than that for ileostomies 1.8 v (0.6–2.7) (p=0.0001)*. In patients with pouchitis (n=12) the flux readings (0.63 v (0.25–1.8) were significantly lower than in patients with healthy mucosa (n=11) 1.17 v (0.6–1.8) (p=0.0046).

A retrospective review of operative notes in these patients showed that vascular division to achieve adequate ileal length is more common in patients with pouchitis but this fails to reach significance in this number of patients. (Pouchitis 60% v no pouchitis 30% (p=0.1)†.

These results suggest that ischaemic may...
be an aetiological factor in the pathogenesis of pouchitis.

* Mann-Whitney U test, † Fisher’s exact test.

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**PAEDIATRICS**

**Campylobacter pylori in families of children with peptic ulcer**

G ODERDA, D VAIRA, J HOLLIN, C AIKLEY, A SMITH, F ALTARE, M BOERO, and N ANSAIDI (Dept of Paediatric Gastroenterology, University of Turin, Italy and Depts of Gastroenterology and Microbiology, Middlesex Hospital, London) Little is known about the source and the spread of Campylobacter pylori (CP), but direct transmission within family contacts has been suggested. We therefore examined the relatives of 10 children, seven with duodenal ulcer (DU) and three with gastric ulcer (GU) (mean age 12 years).

Seven of the index children were CP positive by histology, culture, and urease testing (six DU and one GU), and three were CP negative as assessed by all three methods (one DU, two GU). Serum concentrations of anti-CP IgG, pepsinogen I (PG I), and gastrin (G) were measured in all children and their relatives. All 28 first degree relatives of the seropositive children consented to endoscopy (14 men, 14 women; mean age 32-2 years). Three were found to have DU and 18 were normal; seven had macroscopic antral inflammation. Twenty one of 28 showed histological antral gastritis and in all 21, CP was detected by at least two methods. Endoscopy was performed in the three of seven relatives of CP negative children who had high IgG titres. Two had macroscopic antral gastritis and one was normal at endoscopy, but all three had histological gastritis and the CP. There were no differences in the prevalence of CP, values of IgG titres, and PG I, and G values between the relatives of CP positive and negative children.

This study shows that CP infection is frequent in family groups, although the source and the sequence of infection remains to be established. The study confirms the prospective use of CP IgG titres as a reliable, simple, non-invasive method for diagnosing CP associated gastritis.

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**Campylobacter pylori gastritis and protein losing enteropathy**

P B SULLIVAN, J E THOMAS, P G LUNN, C A NORTHROP-CLEEVES, E J EASTHAM, AND G NEALE (Dept of Child Health, Westminster Children’s Hospital, Vincent Square, London) Campylobacter pylori (CP) gastritis has been reported as being associated with protein losing enteropathy (PLE). In children with chronic diarrhoea and malnutrition (CDM) in the tropics this could have important consequences for nutritional rehabilitation. We have shown a high prevalence of CP infection in infants with CDM in the Gambia on the basis of circulating antibodies (validated by gastric histology and microbiology). In this study we examined the relation between PLE and CP infection in children with CDM using random fecal alpha-1-antitrypsin (FA1-AT) measurements as an index of gut protein loss. Of 53 children with CDM: 30 were CP seropositive (11 gastritis and organism confirmed histologically); 17 CP seronegative; and six were infected with Strongylodes stercoralis. The FA1-AT values were correlated with serum albumin measurements. Hypoalbuminaemia occurring in children infected with S stercoralis was found to be associated (r=0.952, p<0.05) with PLE (FA1-AT, mean (SD) 2.47 (0.94) mg/g stool) whereas there was no correlation in children infected with CP (FA1-AT, 1.57 (0.2) mg/g stool) compared with CDM children without CP infection (FA1-AT, 1.62 (0.3) mg/g stool).

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**Campylobacter pylori gastritis in children: treatment with De-Nol**

M J MAHONY, J I WYATT, AND J M LITTLEWOOD (Depts of Paediatrics and Pathology, St James’s University Hospital, Leeds) Since June 1987 we have diagnosed Campylobacter pylori (CP) associated gastritis in 11 of 51 (21.6%) children who underwent endoscopy for recurrent abdominal pain and upper gastrointestinal symptoms. Seven children (aged, median (range) 13 (5-16) years; five girls, four boys) were treated with De-Nol (tri-potassium dicitrato bismuthate) (240 mg bd) for two months and ampicillin 500 mg qds for two weeks. We have evaluated the effectiveness of this treatment in clearing CP colonisation from the gastric antrum and on altering the severity of gastritis. Antral biopsies were obtained at diagnosis and six weeks after treatment, and were stained for CP using Giemsa. Gastritis was graded from 0-9 in severity using Marshall’s criteria. Serum bismuth values were measured in all children during treatment.

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The symptoms resolved and CP colonisation was cleared in five of seven (71%) children, and the gastritis score fell in all responders from mean 4 to 1.4. The CP colonisation persisted and the gastritis score was unaltered in two children, who remained symptomatic. No child developed signs of bismuth toxicity, and bismuth concentrations were mean (range) 15 µg/l (3-29) (toxic levels >100 µg/l).

Combined treatment with De-Nol and ampicillin is effective and safe in children with CP associated gastritis.

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**Do low serum alpha-tocopherol concentrations in liver damage result from hepatic alpha-tocopherol sequestration?**

I BARROW, S P ASHMORE, H R PATEL, AND M S TANNER (Dept of Child Health, University of Leicester, Leicester) Low serum vitamin E has been attributed to malabsorption in cholestasis and to anorexia in alcoholic liver disease. In two rat models, however, we found evidence of hepatic alpha tocopherol (a-TH) sequestration during liver injury.

After four weeks on a vitamin E deficient diet (0.5 mg/kg; normal 100 mg/kg) rat serum a-TH fell significantly from 8.8 mean (SD) (1.2) to 1.4 (0.3) µg/ml (p<0.001) and the serum ration of a-TH lipid (triglyceride + cholesterol) fell from 1.00 to 0.18 (p<0.001). Hepatic a-TH also fell significantly from 2.89 (3.7) to 3.7 (1.5) µg/g (p<0.001).

Raising the hepatic copper value from 41 (16) to 2659 (858) µg/g by four weeks of dietary copper sulphate supplementation (3 g/kg) caused a significant rise in hepatic a-TH from 28.9 (3.7) to 50.8 (12.1) µg/g (p<0.01) in the vitamin E replete rats. In the vitamin E deficient rats, a comparable increase in liver copper from 43 (9) to 2536 (1115) µg/g also caused a rise in hepatic a-TH from 3.7 (1.5) to 4.8 (1.8) µg/g; serum a-TH fell in the vitamin E deficient rats from 1.4 (0.3) to 0.8 (1.0) µg/ml (p<0.05).

Hepatic copper toxicity was therefore associated with sequestration of a-TH within the liver.

In a study of carbon tetracloride-induced liver damage in rats, the serum a-TH fell from 3.3 (0.2) to 0.6 (0.2) µg/ml and the serum a-TH lipid ratio fell from 0.54 to 0.19. We propose that this fall in serum values is associated with hepatic a-TH retention.

Some caution should therefore be exercised when interpreting low serum vitamin E concentrations in the presence of liver injury. Sequestration of a-TH in the
liver would be an appropriate response to oxidant injury.

**Does sequential caffeine half-life predict deteriorating liver function in children?**

A J BAKER, N BALLANTINE, and D A KELLY (Liver Unit, Birmingham; Children’s Hospital, Birmingham) Liver transplant is accepted treatment for end stage liver disease in children, but the limited availability of donors makes selection of patients critical. In this study we performed sequential-salivary caffeine half-life tests (SCT½) after a single dose of 3 mg/kg oral caffeine. These were compared with serum albumin, prothrombin time (PT), total bilirubin, and to mid-arm muscle area (MAMA) to determine which showed earliest deterioration of liver function. Some 53 tests were performed on 14 children with cirrhosis and portal hypertension (aged 4 months to 15 years). All were evaluated for liver transplant.

Regression analysis showed SCT½ and PT to be interdependent. As SCT½ is not vitamin K dependent it may reflect hepatocellular function more accurately and provide earlier evidence of deterioration. Sequential SCT½ measurements provide additional information when selecting children for transplantation.

**Hepatobiliary ultrasound in cystic fibrosis – findings in 201 patients related to biochemical parameters**

J SMITH, H PATRIOQUIN, C LENAERTS, C C ROY, I YOUSEF, and A M WEBER (Depts of Pediatric Gastroenterology and Radiology, Hôpital Ste-Justine, Montreal, Quebec, Canada) Hepatobiliary manifestations of cystic fibrosis are common, and the incidence of clinical disease reaches 10% by adulthood. A prospective study of hepatobiliary ultrasound (US) was carried out in 201 patients aged 1–21 years. On the same day standard liver function tests, gGT, pre- and post-prandial serum bile acids (BA), and a caffeine tolerance test were undertaken. Forty four patients (21%) had an abnormal liver sonogram: 17 (7%) had hyperecho- genicity suggestive of steatosis, and 19 (9.4%) had a heterogeneous pattern suggestive of cirrhosis, in whom half had signs of portal hypertension. Biliary tree examination showed 47 patients (23%) with a microgall bladder and 16 (8%) had cholelithiasis. Two patients showed dilatation of intra- or extrahepatic bile ducts.

Multiple logistic regression analysis showed that the gGT, BA, ALT, and meconium ileus or its equivalent were important factors determining an abnormal ultrasound. A total of 50% of those with US evidence of steatosis, and 75% of those with presumed cirrhosis had abnormalities of liver enzymes.

Ultrasound evidence of liver disease may be a sensitive marker of early involvement. We suggest that US should be part of the periodic assessment of cystic fibrosis patients.

**Scanning electron microscopy appearances of jejunal mucosa in children with non-specific (toddler) diarrhoea**

P McCLEAN, S NUNN, K CARR, and J A DODGE (Depts of Child Health and Anatomy, The Queen’s University of Belfast) Jejunal biopsies were obtained from seven children with toddler diarrhoea (TD) and eight children with no gastrointestinal symptoms who were investigated for short stature or failure to thrive. A double port paediatric intestinal biopsy capsule was used and the two samples obtained were processed for light microscopy (LM) and scanning electron microscopy (SEM). Where possible, jejunal juice was obtained for culture.

The LM showed normal mucosal architecture, and culture of jejunal juice produced no growth of organisms in either group. Using the SEM and computerised morphometric techniques, however, the biopsy specimens from children with TD showed a significantly greater unit area/villi (0.15 mm²) than the control group (0.05 mm²). Two of eight biopsy specimens from the control group showed the presence of micro-organisms on the mucosal surface whereas micro-organisms were identified on the surface of every biopsy specimen taken from the children with TD.

These results suggest that bacterial contamination of the small intestine may play a role in the pathogenesis of TD.

**Assessment of hypertonic oral rehydration solutions in an animal model of secretory diarrhoea**

J B HUNT, S CARNABY, and M J G FARTHING (Dept of Gastroenterology, St Bartholomew’s Hospital, London) Although the efficacy of oral rehydration solution (ORS) in the treatment of secretory diarrhoea is established, its optimum formulation has not been determined. We have previously shown greater water and similar sodium absorption from a hypotonic (240 mOsm/kg) ORS (ORS-240) and WHO-ORS in normal human jejunum by triple lumen perfusions. We have now studied a range of hypotonic ORSs in a secretory model in vivo which incorporates perfusion of entire rat small intestine pretreated with cholera toxin. We have examined absorption of water and sodium from four hypotonic ORSs all of which contain glucose 90 mmol/l with sodium ranging between 45 and 75 mmol/l, giving final osmolalities of 210–270 mOsm/kg. These ORSs were compared with WHO-ORS (Na 90, bic 23, glu 90 mmol/l) and a standard UK-ORS (Na 35, bic 18, glu 200 mmol/l). All HYPO-ORS produced significantly greater water absorption than WHO-ORS and UK-ORS (p<0.01). Water absorption was greatest with ORS-210 (mean (SD) 113-6 (16-7) µl/g/min; n=6) compared with WHO-ORS (14-8 (4-8); n=6; p<0.01). Sodium secretion occurred with all solutions, being least with the relatively high sodium WHO-ORS.

Thus, HYPO-ORS promote greater water absorption than standard ORS, although sodium absorption is reduced. Since water deficit is greater than sodium deficit in non-cholera diarrhoea, HYPO-ORS may have clinical advantages in rehydration.

**Small intestinal motor activity response to cisapride in children with dysmotility syndromes**

R C COOMBS and J W BOOTH (Institute of Child Health, Birmingham) Small intestinal dysmotility is uncommon in childhood, but is difficult to treat and may be the cause of substantial morbidity. We have studied the effects of cisapride (CIS; 2 mg/kg per dose, by suppository) on small intestinal motor activity in four patients, three with pseudo-obstruction and one with intestinal hyperganglionosis (age, median (range) 17 weeks (3–104), using an intraluminal three channel, solid state pressure transducer. Two patients were dependant parenteral nutrition (PN) and three had an associated malrotation. All four patients had non-propagated motor complexes (MC), one had sustained tonic increases in intraluminal pressure (>20 mmHg), and another had continuously disorganised motor activity.

After CIS there was a significant improvement in the number of propagated MC (from 40/66 pre-CIS to 55/67 post-CIS: p<0.01), and a fall in the number of tonic
Anorectal function in children with severe cerebral palsy

U Agnarsson, C Gordon, G McCarthy, N Evans, and G Clayden (Royal Alexandra Hospital for Sick Children, Brighton and St Thomas’s Hospital, London) To assess bowel function in children with cerebral palsy (CP), 28 patients, 16 boys and 12 girls, aged mean (range) 9-5 years (3-16) had anorectal manometry performed. Twenty three patients had spastic quadriplegia, three had athetoid with or without spastic CP, and two had mixed forms. Controls consisted of 24 non-uretic children. Portable anorectal manometry equipment was used comprising a computer linked via pressure transducers to an anal probe with three water-filled anal sensor balloons (b1, b2, and b3) and a terminal 200 ml air filled balloon.

The resting pressure in all three anal balloons was similar in patients and controls (mean (SD) pressures in mmHg). CP results given first b1: 47-9 (16-2) vs 52-3 (18-4); b2: 40-3 (18-5) vs 35-7 (15-3); b3: 19-2 (14-3) vs 13-0 (9-3). Maximal resting pressure was 65-6 (15-2) vs 64-4 (19-7). An indirect assessment of rectal size can be gained by observing the change in anal pressure in the innermost balloon (b3) during maximal rectal distension. In CP the pressure fell but increased in controls (3-2 (12-0) vs 9-2 (15-2), p<0.001). Rectal sensation was normal in 64%, reduced in 29%, absent in 5-3%, and uncertain in 3-5% of patients compared with normal in 82% and reduced in 18% of controls. The frequency of anal rhythmic activity was on average slower in patients than controls (11-13 vs 12-14 waves/min), and 49% of patients had a frequency of 9 waves/min or less compared with 25% of controls.

In CP, anal pressures are normal but the frequency of anal rhythmic activity varies more than normal suggesting altered dynamics of the internal anal sphincter.

Rectal sensation is reduced and rectal size is increased, which may explain why constipation seems to be common in children with CP.

ENDOSCOPY

Endoscopic Nd-YAG laser therapy for benign disease of the colon and rectum

F N Brennan and B H Laurence (Gastroenterology Liver Unit, Sir Charles Gardiner Hospital, Nedlands, Western Australia) Large sessile polyps or coagulopathies increase the risk of endoscopic polypectomy by snare diathermy. Local surgical removal has an appreciable morbidity and there is a high recurrence rate. Endoscopic laser photocoagulation is an accepted method for treating luminal tumour in obstructing malignancy and can be used for removing polyps in high risk patients.

Thirty one patients with colonic adenomas (25 rectal) have been treated by this method – 19 with broad based polyps considered unsuitable for diathermy, seven with polyp recurrence after subtotal colectomy for polyposis coli, and four with major coagulopathies (anticoagulants, Von Willebrand's disease). An Nd-YAG laser (MBB) was used (multiple 0-5 sec 50 watt pulses) with conventional colonoscopes. For large polyps, several sessions were required. Obliteration of the polyp was achieved in 20 patients (83%), two required surgery (one for severe atypia) and one piecemeal diathermy removal. There were no major complications. There have been four recurrences (21%) between 19 and 28 weeks after treatment: all were treated again by laser coagulation. Four patients have been lost to follow up and the remainder are clear at an interval of median (range) 18 months (2-31).

Laser photocoagulation is an effective alternative where traditional polypectomy is technically difficult; longterm follow up of the patients is necessary.

Acceptability of endoscopy and colonoscopy – patients' views

B Ives, J K Ramage, B Wright, and R J Leicester (Dept of Gastroenterology, Royal Naval Hospital, Haslar, Hampshire) Patient care in endoscopy departments is often organised without reference to information obtained from them. A questionnaire was distributed to 235 consecutive patients attending one department to assess patients' views. KeyMed information leaflets had been issued and patients received 5 mg midazolam with no throat spray (for endoscopy) and 30 mg pentazocine plus 7.5 mg midazolam (colonoscopy). A total of 169 replies could be analysed (124 for endoscopy, 45 for colonoscopy). In patients who received leaflets for endoscopy, 98 found them excellent or very good, 11 reasonable, and one poor; for colonoscopy, 40 found them excellent or very good and four reasonable. Six patients found difficulty with the preparation for colonoscopy and 10 difficulty with the overnight fast for endoscopy. Altogether 18 endoscopy and eight colonoscopy patients remembered all or most of the procedure, and these felt fewer pain afterwards: four suggested an increased amount of sedation. The sedation affected patients for a mean (range) of 3-14 hours (0-24) after endoscopy and 6-24 hours (0-48) after colonoscopy. After endoscopy, 20 patients experienced pain, 25 a sore throat, and four a headache. After colonoscopy 18 experienced abdominal pain.

Audit of patients’ views leads to useful adjustments to a department's policies.

How to reduce endoscopic workload for detection of dysplasia after gastric surgery

R S Savalgi, C Corbishley, C Caygill, M Hill, J S Kirkham, M Cook, and T C Northfield (Norman Tanner Gastroenterology Unit, St George’s Hospital and Medical School, London) Our epidemiological studies have shown that sex, type of ulcer, and type of operation influence the risk of developing gastric cancer after gastric surgery. Our aim has been to identify a high risk subgroup for endoscopic screening by assessing whether these three factors also influence the risk of developing gastric dysplasia.

Eighty seven subjects who had had gastric surgery >20 years ago underwent endoscopy. Gastric biopsy specimens (n=12; stoma, six; body, six) were graded for severity of dysplasia. The frequency of dysplasia in BI subjects (n=52, nil=15%, mild=48%, moderate or severe=37%) was higher (p<0.001) than for other operations (BI or vagotomy and drainage, n=35, nil=50%, mild=40%, moderate or severe=10%). Within BI subjects, the frequency of moderate or severe dysplasia was significantly higher in the stoma (35%, p<0.01) than in the body (10%). Sex and type of surgery were not significant factors.
ulcer did not influence the frequency of dysplasia.

We conclude that the type of operation affects the frequency of dysplasia. Had we limited endoscopic screening to BI subjects only and taken stomal biopsy specimens only, we would have achieved a 40% reduction in the number of endoscopies and a 70% reduction in the number of biopsy specimens, with only a 15% reduction in the detection of moderate and severe dysplasia.

GASTRODUODENAL III

Comparison of symptoms between non-ulcer dyspepsia patients positive and negative for Campylobacter pylori using a single bias computer system for history taking

J S A Collins, R P KhiJ-Jones, J M Sloan, P C H Watt, P W Hamilton, G P Crean, and A H G Love (Dept of Medicine, The Queen's University of Belfast, and Diagnostic Methodology Research Unit, Southern General Hospital, Glasgow) The role of Campylobacter pylori (CP) infection in the symptom complex associated with non-ulcer dyspepsia (NUD) is uncertain, despite the presence of the organism in a high proportion of these patients. In order to exclude physician bias in history taking, 18 patients (nine men, nine women) diagnosed as NUD after endoscopy and gall bladder ultrasonography, completed a computer interview with the Glasgow diagnostic system for dyspepsia (GLADYS). Five antral and three fundal endoscopic biopsy specimens were also independently assessed for CP and morphometrically analysed for polymorph and chronic inflammatory cell densities per mm² of lamina propria.

In the group of nine of 18 patients who were CP positive, three were significantly higher antral and fundal inflammatory cell counts than in CP negative patients. Analysis of the GLADYS data, however, showed no significant positive correlations between CP positivity and any gastrointestinal symptoms. No symptom was significantly more frequent in the CP positive patients.

These results confirm a significant association between CP and superficial gastritis but suggest that NUD in patients with CP colonisation is probably not a clinically identifiable and distinct syndrome.

Gastric cancer in Scotland: a halt in the decline?

D M Sedgwick, J A Koh, J A Clarke, and I M C MacIntyre (Surgical Review Office, Western General Hospital, Edinburgh and Common Services Agency, Trinity Park House, Edinburgh) For the past 40 years the incidence of gastric cancer has been falling throughout the world. In Scotland the mortality rates fell from 75/10³ population in 1940 to 52/10³ population in 1970. Since 1980 this fall has plateaued; 42/10³ in 1980 and 39/10³ in 1987. Scottish cancer registry data have been examined for the 17 year period 1971–1987. These showed no decline for either sex in the numbers of gastric cancers registered. The incidence per 10³ population has also remained static. Applying age standardisation to registration figures there has been a relative decrease in those <65 years and a relative increase in those >70 years old between 1971 and 1987. Even in our own unit the referral rate has not changed between 1975 and 1985. These figures seem to show that although Scotland paralleled the worldwide natural history of gastric cancer before 1970, since then the fall has ceased. This has implications for screening for early gastric cancer and in surgical and oncological workloads.

Longterm survivors of Nd:YAG laser therapy for upper gastrointestinal carcinoma

P T Chatlani, H Barr, and N Krasner (Walton Hospital, Liverpool) Between September 1981 and November 1988, 286 patients were referred for endoscopic Nd:YAG laser palliation of carcinoma of the oesophagus or gastric cardia. Mean (SD) survival was 21.5 (23.6) weeks, and 35.0% subsequently, or had previously, received adjuvant therapy. The characteristics of the longterm (>26 weeks) survivors (survival=46.8 (24.0) weeks) (n=93) have been studied and five groups identified: laser alone (L) (n=50), laser followed by tube placement (L+T) (n=20), laser treatment of tube complications (TC+L) (n=8), laser followed by chemotherapy, radiotherapy or surgery (L+CXS) (n=8), and laser treatment of recurrence after surgery (S+L) (n=seven). The L+T group includes those in whom the laser was used initially but intubation was subsequently performed, either because the tumours were too long or bulky to palliate satisfactorily with laser alone or because the decision was taken to limit further laser treatment. This group had the longest structures (9.2 (3.6) cm). Furthermore, this group (L+T) together with the TC+L group were associated with the shortest survival (36.4 (8.9) and 39.7 (11.4) weeks, respectively). In contrast, the S+L (predominantly adenocarcinomas in younger patients) and L+CXS groups were associated with longest survival (57.9 (29.8) and 58.0 (27.1) weeks, respectively). The survival of the L group was intermediate (47.7 (24.8) weeks).

Nd:YAG laser therapy forms a useful basis for palliation, but the enhanced survival with adjuvant therapy indicates the need for the development of a therapeutic protocol, optimally combining treatment modalities and taking cognisance of tumour characteristics and the individual patient’s needs.

Human immunodeficiency virus can be found within the gastric mucosa in association with histological gastritis in patients with AIDS

P D Edwards, J Turner, E Vasak, K Christopoulos, and D G Cooper (Depts of Gastroenterology and Histopathology, St Vincent’s Hospital, Sydney, Australia) This study aimed to determine whether the presence of human immunodeficiency virus (HIV) within the gastric mucosa is associated with histological gastritis in patients with AIDS.

Gastric biopsies, from 41 AIDS patients with non-specific histological gastritis were examined by an avidin/biotin immunoperoxidase method, using monoclonal antibodies to the p18, p24 core proteins and the Gp41 envelope protein of the HIV (Genetic Systems). HIV infected cells from a Hutt 78 T cell line were prepared as thrombin cell blocks and used as positive controls. Gastric biopsy specimens from HIV negative patients with and without histological gastritis were used as negative controls.

Ten of 41 patients (24%) had positive immunoperoxidase staining for the presence of HIV within the gastric mucosa. In all of these subjects there was an associated histological gastritis. In eight of the 10 positive subjects the staining was predominantly in the endothelium, of small blood vessels in the lamina propria (p18 antibody). One patient had positive staining of the glandular epithelium while another had positively staining macrophages within the lamina propria (all antibodies).

In a significant number of AIDS patients with non-specific histological gastritis, there is evidence of the HIV within the gastric mucosa. The predominant site of infection is in the endothelium. Glandular epithelial
cells and macrophages within the gastric mucosa may also be infected.

Acute upper gastrointestinal bleeding in patients with AIDS: a relatively uncommon clinical manifestation

G BIANCHI PORRO, F PARENTE, AND M CERNUSCHI (Depts of Gastroenterology and Infectious Disease, L Sacco Hospital, Milan, Italy) The exact prevalence of acute upper gastrointestinal (GI) bleeding in AIDS is still uncertain. Some 483 patients with AIDS, diagnosed in our hospital between June 1985 and March 1989, were followed up for a median (range) time of 6 months (0.5-42). Fifteen patients presented with one or more episodes of haematemesis or melena, or both, but an emergency upper GI endoscopy was feasible in only 10. Seven patients were found to have AIDS related GI pathologies: gastric or duodenal lymphoma, or both, (three), candida oesophagitis (one), HSV oesophagitis with candida superinfection (one), cytomegalovirus oesophagitis (one), MAI duodentis (one); three patients were shown to bleed from non-AIDS related lesions: benign gastric ulcer (one), oesophageal varices (one), and duodenal ulcer (one). Although GI Kaposi's sarcoma lesions are believed to frequently bleed, spontaneously or after biopsy, in our population this event seems to be very rare; in fact in 20 patients with digestive involvement, no cases of haemorrhage from these lesions were observed.

We conclude that the prevalence of acute GI bleeding in AIDS is low (3-1%) and in most of the cases it results from conditions specifically associated with the disease. As many of the causative disorders are potentially treatable, an aggressive diagnostic approach is indicated, except for those patients who are terminally ill.

Hepatitis B virus infection in non-cirrhotic hepatoma

C KALAYCI, P J JOHNSON, AND R WILLIAMS (Liver Unit, King's College Hospital School of Medicine and Dentistry, London) The extensive evidence linking hepatitis B virus (HBV) infection with the development of hepatocellular carcinoma (HCC) is confounded by the even stronger association of hepatic cirrhosis with HCC in low incidence areas and the equally strong association in high incidence areas. One way of overcoming this problem is to study HBV infection in HCC patients without cirrhosis in a country where the natural prevalence of HBV markers is very low.

We have measured serum HBV markers in 137 consecutive patients with HCC (95 born and raised in the UK, 42 from overseas) in a non-cirrhotic liver. Of these, 137, seven (5%) were HBsAg seropositive and six came to operation or necropsy so that the absence of cirrhosis could be confirmed directly. Five of the seven were anti-HBe seropositive, one was HBeAg positive, and one had no 'e' markers. Two had the fibrolamellar variant, but none had any recognisable risk factors, other than birth in an area of high HBV prevalence in four. Of the HBSAg positive patients came from the UK, and this represents an overall figure of 3% HBsAg seropositivity compared with a carriage rate of <0-1% in the normal population. The frequency of anti-HBs (7.5%) and anti-HBc alone (7%) in the HCC patients was also higher than that seen...
in the normal UK population (2.4% and 2.1% respectively).

HBV infection seems to be a small but significant risk factor for the development of HCC even in the non-cirrhotic group.

Sequential haemodynamic changes during single total paracentesis and right atrial size in patients with tense ascites

M Panos, K Moore, P Llavanos, J Chambers, J Anderson, A Gimson, D Westaby, and R Williams (Liver Unit, King's College Hospital and School of Medicine and Dentistry, London) - Haemodynamic changes induced by a single, total paracentesis were evaluated in 21 patients with tense ascites in whom four to 16 l of ascites were drained over two to eight hours, with no serious complications. At 60 minutes, compared with baseline, there was a significant drop in right atrial pressure (9.3 (0-8) to 7.50 (0-8) mmHg (p<0.02) and an increase in cardiac output (7.7 (0-5) to 8.5 (0-6) l/min. p<0.02), with no change in pulmonary capillary wedge pressure (10.9 (0-9) to 10.7 (0-9) mmHg). At two hours, the concentration of plasma atrial natriuretic peptide increased (8.9 (1-18) to 10.25 (1-2) pmol/L, p<0.05, n=12), consistent with increased venous return and atrial distension with improved right sided cardiac function. Subsequently, between three and 12 hours, there was a drop in right atrial pressure, pulmonary capillary wedge pressure, and cardiac output to 5.6 (0-6) l/min. at 7.2 (0-6) l/min (NS) respectively, indicative of the development of hypovolaemia and pointing to the need for therapeutic plasma expansion at this time. 2D echocardiography in eight patients before paracentesis showed a reduction in the right to left atrium area ratio compared with values in eight patients with cirrhosis and minimal ascites (0.54 (0-04) vs 0.82 (0-02), p<0.0001).

These results suggest that in patients with tense ascites, venous return may be impaired due to compression of the right atrium. It is possible that 2D echocardiography may help in identifying these patients.

Effect of severe haemorrhage on collateral blood flow in rats with cirrhosis and portal hypertension

J Yates, D Nott, S Ellenbogen, T Cooke, S Jenkins, and R Shields (University Dept of Surgery, Royal Liverpool Hospital, Liver-pool) Although severe haemorrhage in the cirrhotic rat constricts the splancnic vessels and reduces portal pressure, its effect on collateral blood flow, especially varical blood flow, is not known. Therefore, we have undertaken such a study in cirrhotic rats.

Rats with dimethylnitrosamine induced cirrhosis and portal hypertension were bled at a constant rate from a femoral artery. Arterial blood pressure (ABP) and portal pressure (PP) were monitored continuously throughout the study, and collateral blood flow was measured by consecutive intrasplenic injection of 51Cr-methylene diphosphonate and 131I-albumin microspheres before and after haemorrhage.

With haemorrhage there were significant decreases (p<0.001; Student's paired t test) in mean ABP (118.9 (13-4) to 46.0 (8.3) mmHg) and PP (14.5 (1.3) to 6.9 (0.5) mmHg). In contrast, haemorrhage resulted in a significant increase (p<0.01) in collateral blood flow (8.0 (1.3) to 14.1 (1-1)%).

This study clearly indicates that collateral blood flow increases after severe haemorrhage in cirrhotic rats, possibly due to a rise in intrahepatic resistance. These results explain why bleeding from varices may persist in some patients despite massive blood loss and suggest that to be successful, vasoactive drugs must reduce collateral blood flow.

Recovery of the rectoanal inhibitory reflex after low stapled colorectal anastomosis

M G O Riordan, R G Molloy, P Gillen, and W O Kirwan (University Dept of Surgery, Regional Hospital, Cork, Ireland) - The rectoanal inhibitory reflex plays an important role in the normal mechanisms of anorectal continence. Rectal distension, either by stool or artificially by a balloon, causes reflex relaxation of the internal anal sphincter allowing rectal contents to pass into the upper anal canal, thus facilitating sampling by the sensitive anal mucosa. It is accepted that the reflex is abolished by low anterior resection (AR), but whether it recovers, particularly after stapled anastomosis, is not known.

Fifty six patients undergoing low stapled AR for rectal carcinoma were studied. The resting anal sphincter pressure was measured using a station pull through technique, and the reflex inhibition of the resting tone after the inflation of a 50 ml rectal balloon was determined. In the post-operative patients, care was taken to ensure that the balloon was placed above the anastomosis.

Forty two patients were studied peri-operatively. The reflex was present in 41 (98%) preoperatively, but in only five (12%) 10 days postoperatively. In only three of 25 patients (12%) studied between six months and one year postoperatively was the reflex found, and in two of these the reflex had been present immediately after operation. In 17 patients, the reflex was studied more than two years postoperatively and in 15 of these (87%) the reflex was found.

In a small proportion of patients, the reflex is not abolished by low AR, but in the...
Evaluation of a simple scoring system to assist diagnosis of diarrhoea in patients with AIDS

A FORRES, G M CONNOLLY, J SMITHSON, J RUSSELL, AND G GAZZARD (Dept of Gastroenterology, Westminster Hospital, London)

Diarrhoea is a common problem in patients infected with human immunodeficiency virus (HIV-1); identifiable pathogens are usually scored, but not always with case. Prospective data from a comprehensively studied group of patients with HIV-1 and chronic, apparently pathogen negative diarrhoea, suggested that the degree of weight loss and abnormality of Schilling test together, were sufficient to predict whether a responsible pathogen would be found or not. Points (modified Bayes theorem) can be allocated as follows: weight loss <5 kg; 0; 5-10 kg; 1 >10 kg; 2; Schilling excretion >5-5 kg; 0; ≤5-5%: 2. The baseline data predict ≤5% fatal pathogen recognition for a score of 0–2; 50% for a score of 3; 90% for a score of 4. The scoring system has now been applied prospectively to unselected HIV-1 positive patients presenting with diarrhoea. In no patient with a score of <3 has a pathogen been identified despite thorough investigation; to date all patients with a score of 4, and 86% of those with a score of 3, have been found to have pathogens.

The scoring system is therefore validated, and it is suggested that since useful information is unlikely to emerge, patients with a score of less than 3 need no investigation beyond the routine study of three stool samples and rectal histology.

Full thickness anorectal advancement flaps in the treatment of trans-sphincteric fistulae

P LEWIS AND D C BARTOLO (University Dept of Surgery, Bristol Royal Infirmary, Bristol)

‘Laying open’ high trans-sphincteric fistulae may cause incontinence and the resulting cavity heals poorly in patients with Crohn’s disease. In order to avoid these problems we have used an anorectal advancement flap technique. Six patients, comprising three men and three women with a mean age of 35 years (range 18–67 years), were referred with high transsphincteric fistulae.

Four patients had Crohn’s disease, two with terminal ileitis and three proctocolitis. None of these patients underwent excisional abdominal surgery, but proctitis was rendered inactive by medical treatment. Two patients with idiopathic fistulae had previously been treated by a ‘lay open’ technique, but had developed recurrent double horseshoe tracks.

In each patient, a full thickness flap of half the circumference of the posterior rectal wall was excised posteriorly. The internal opening of the track was closed and covered by anastomosing the mobilised rectum to the anal canal.

Complete healing occurred in six patients with no deterioration in continence. The mean duration of hospital stay was 6 days (range 5–9 days) and the average time to resolution of the perineal component of the fistula was nine weeks. In one patient with an idiopathic double horseshoe track the fistula recurred and a further anorectal advancement flap procedure has been performed.

We conclude that even in patients with Crohn’s disease, trans-sphincteric fistulae may be successfully treated without sphincter division by an advancement flap technique.

Palliation for incurable recto-sigmoid cancer: surgery or laser?

I A LOIZOU, V KOMBOROZIS, S G BROWN, AND P B BOULOS (University College Hospital, London)
The appropriate management of incurable rectosigmoid cancer is unclear. We retrospectively analysed the outcome of 47 patients treated surgically (1978–1987) and compared this with 42 patients managed prospectively by endoscopic Nd:YAG laser therapy (1986–1988). The groups were matched for sex, symptomatic presentation, and tumour location, although laser patients were older (mean 73 v 66 years, p<0.05). Thirty eight (81%) surgical and 19 (45%) laser patients had hepatic metastases (p<0.001); the remainder had advanced local disease. Thirty four (72%) surgical patients underwent resection (anterior: 16, abdomino-perineal: 13, Hartman’s: five) and 13 (28%) had a defunctioning colostomy. The local palliation rate with laser therapy was 74% (obstruction: 67%, rectal discharge and tenesmus: 78%). Surgery was associated with greater mortality (8.5% v 0%, p<0.001), morbidity (43% v 7%, p<0.001), and hospital stay (40 v 9 days, p<0.001), although survival was longer (7.7 v 4.6 months, p<0.05). Patients undergoing resection survived significantly longer than those managed by defunctioning colostomy or laser therapy (mean 9.3 v 3.2 v 4.6 months; p<0.005). The difference was mainly in patients with liver metastases (mean survival for resection 10, colostomy 2–7, and laser 4–8 months) and was not seen in patients with locally advanced disease (mean survival for resection 5–4, colostomy 4, and laser 4–4 months).

For locally advanced disease, laser therapy is preferable. Controlled studies are required for those with hepatic metastases as the patient groups were probably not comparable.

Colorectal II

Surgical treatment of anorectal disease

A J G MILES, C H MELLOR, B G GAZZARD, T G ALLEN-MERSH, AND C WASTELL (Depts of Surgery and Gastroenterology, St Stephen’s Hospital, London)

Anorectal disease is the most frequent indication for surgical referral of HIV positive homosexual men by AIDS physicians. We have assessed the prevalence, nature, and outcome of surgical treatment of anorectal disease in 1090 HIV positive homosexual men seen at one hospital over a nine year period.

Six per cent (64 of 1090) of patients were referred for a surgical opinion concerning anorectal symptoms. There was no significant difference in the stage of HIV disease between patients referred (HIV and PGL 58%, ARC 16%, AIDS 25%) compared with the study population (HIV and PGL 43%, ARC 42%, AIDS 15%). A diagnosis was made in 95% (61 of 64) of patients: anal warts 38%, anorectal ulceration 26%, perianal sepsis 15%, malignant neoplasia 14%, haemorrhoidal disease 7%. Eighty five per cent (54 of 64) of patients underwent surgical treatment. Symptoms were relieved in 73% (47 of 64). Median survival of patients after surgical treatment was 17.5 months.

The relative risk of anorectal disease requiring surgery was 14 times that of the adult male population of England and was not solely related to immunodeficiency. Conditions encountered were unusual and there was a high incidence of malignant neoplasia. Surgical treatment offered good palliation in most cases.
Reproducibility and measurement of segmental colonic transit using radio opaque markers

D J WALDRON, D KUMAR, R I HALLAN, D I WINGATE, AND N S WILLIAMS (Surgical Unit and GI Science Dept, The London Hospital, London) Reproducibility of colonic transit studies and the measurement of segmental transit are essential for the understanding and treatment of idiopathic severe constipation. We have studied whether the standard method—that is, ingestion of inert markers—is reproducible and can accurately determine segmental transit.

Different shaped radiopaque particles were ingested by 12 patients with intractable constipation (not receiving laxatives) at intervals over 100 hours before a single x-ray (rods at 100 hours, circles at 72 hours, triangles at 24 hours). The study was repeated two weeks later to assess reproducibility of the position of each marker type. There was a positive correlation between the number of markers ingested 100 hours before x-ray with regard to those evacuated (r=0.65; p<0.05), in right (r=0.94; p<0.001), and left (r=0.72; p<0.01) colon in the two studies. The segmental transit of markers ingested 72 and 24 hours before x-ray did not correlate between studies except in the left colon at 72 hours (r=0.6; p<0.05) and rectosigmoid at 24 hours (r=0.75; p<0.01).

Assessment of transit in the colon as a whole, using inert markers is reproducible but not at the shorter intervals of time necessary to assess segmental transit.

Cephalic phase of motilin, pancreatic polypeptide, and gastrin release is associated with the cephalic phase of the colonic response to food, in the acid suppressed stomach

J ROGERS, A H RAIMUNDO, J J MISHEWICZ, AND S R BLOOM (Dept of Gastroenterology and Nutrition, Central Middlesex Hospital and Dept of Endocrinology, Royal Postgraduate Hospital, Hammersmith, London) To determine whether gastrointestinal hormones can be released by cephalic stimulation, and whether this is associated with the cephalic phase of colonic response to food, plasma was sampled in eight normal subjects (seven men, one woman; mean (SD) age 20-6 years (9-7)), undergoing studies of colonic pressure activity. Samples were taken at 30 minutes before, and 15, 30, and 60 minutes after, the start of a 30 minute food discussion (FD) – a cephalic stimulus. Subjects studied on two separate occasions were premedicated in random order with ranitidine 1200 mg, or placebo 14 hours before study. Motilin, gastrin, pancreatic polypeptide (PP), CCK, and neurotensin (NT) were assayed by RIA. Acid output was completely blocked by ranitidine in contrast with low intragastric pH in placebo studies. In the absence of acid, there was a significant (p<0.03) Student’s paired t test) increase in mean (SEM) plasma motilin concentration during (49-8 (7-3) pmol/l, and after (42-2 (5-2)) the FD stimulus compared with basal values (29-8 (3-3)). There were similar significant (p<0.01) increases in plasma gastrin and PP concentrations during FD compared with basal values (15-2 (2-8) pmol/l v 9.3 (2-0); and 24-6 (1-6) pmol/l v 19.3 (1-1), respectively). After FD plasma CCK and NT decreased non-significantly. This response was associated with a cephalically induced significant (p<0.02) increase in colonic pressures.

These data show that there is a cephalic phase to the release of motilin, gastrin, and PP and suggest a possible mechanism for the cephalic phase of the colonic response to food.

Characterisation of rectal flatus

J TOMLIN, C LOWIS, AND N W READ (Sub-Dept of Human Gastrointestinal Physiology and Nutrition, Royal Hallamshire Hospital, Sheffield) Flatus can cause discomfort and distress but there are few data regarding normal patterns and volumes. Twenty four hour collections were made using a rectal tube in 10 normal volunteers taking their normal diet plus 200 g baked beans. Total daily volume ranged from 476 to 1491 ml (median 705 ml). Women (five) and men (five) expelled equivalent amounts. The nocturnal production rate ranged from 2 to 89 ml/h (median 18 ml/h) but was significantly lower than the daytime rate (median 34 ml/h). More collections >60 ml/h occurred in the hour after a meal than the hour before (13 v 5). Median flatus hydrogen content was 57-7% (range 7-2–87-6%), carbon dioxide was 10-5% (range 3-6–13-0%), three volunteers produced methane (0-01, 4-7, and 8-0%), and the remainder unidentified (probably nitrogen) contributed 33-2% (range 8-8 to 81-6%).

Ingestion of a fibre free diet (Fortisip) for 48 hours significantly reduced total volume (median 214 ml/day), carbon dioxide content (median 3-6%), and practically eradicated hydrogen production. The volume of unidentified gas was not significantly affected (208 v 213 mlday) but its contribution rose to 96% (median).

Thus fermentation gases make the highest contribution to flatus. A fibre free diet eliminates these without changing residual gas release of around 200 ml/day.

Symptom ranking in irritable bowel syndrome

D G MAXTON AND P J WHORWELL (Dept of Medicine, University Hospital of South Manchester, Manchester) Although abdominal pain, distension, and abnormal bowel habit are regarded as the cardinal symptoms of irritable bowel syndrome (IBS), additional ‘non-colonic’ features often occur. This study assessed the relative importance to the patient of all IBS associated symptoms.

One hundred consecutive IBS patients identified their symptoms from a list of 14 IBS related features. The six most severe were ranked in order of severity to determine the single worst symptom and calculate a mean rank score. Patients were also assessed psychologically.

Pain, distension, or disturbed bowel habit was the worst symptom in only 56%. A ‘non-colonic’ symptom was the most intrusive in the remainder. Mean rank scores confirmed pain (score: 3-80) and bowel disturbance (3-34) as the most disruptive overall symptoms, but lethargy (2-99) was rated higher than distension (2-82). Backache (2-29), excess wind (2-67), and nausea (2-16) were also prominent. Some symptoms such as early satiety (0-55) were frequent but not severe. The ranking pattern was not affected by psychopathology.

The single worst symptom of IBS may be a ‘non-colonic’ feature leading to inappropriate referral and investigation. Recognition of this helps diagnosis, assists management, and is critical to overall assessment during clinical trials.

**Oral Crohn’s disease, a five year experience of 28 cases**

A J K WILLIAMS, D WRAY, AND A FERGUSON (Depts of Gastroenterology and Dental Surgery, Western General Hospital, Edinburgh) Oral involvement is a rare...
manifestation of Crohn’s disease that is often misdiagnosed at first and whose natural history and treatment is not well defined. We have reviewed the clinical characteristics of 28 patients with oral Crohn’s disease seen in a five year period.

The macroscopic features consist of labial swelling (17), mucosal cobblestoning (11), linear ulcers (11), lumps (five), and mucosal tags (two). Eleven had multiple features. Histology showed non-caseating granulomata (50%) and chronic inflammatory cell infiltrate.

The mean age of patients was 34 years (range 14–74 years); there were 15 males and 13 females. The mean follow up was four years and duration of oral symptoms before diagnosis was 12 months to 10 years (eight developed symptoms in first decade of life). Thirteen have Crohn’s at other sites (10 perianal, five ileal, two colonic), and in seven oral disease was the first manifestation.

Aggravating factors reported include cold weather, trauma, spices, and pepper.

Seven patients have received no specific treatment. Five were prescribed topical corticosteroids, 12 systemic corticosteroids and two azathioprine. Three patients are steroid dependent.

Oral Crohn’s disease has a defined macroscopic appearance which can occur in the first decade of life, and be the first or only manifestation of Crohn’s disease and may require treatment with oral corticosteroids.

Oral fluticasone propionate in active Crohn’s disease

M CARPANI DE KASKI, M PETERS, J P LAVENDER, AND H J F HODGSON (Dept of Medicine and Nuclear Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London) An effective oral corticosteroid, without systemic side effects such as inhibition of the pituitary-adrenal axis or acceleration of osteoporosis, would form a major advance in the treatment of Crohn’s disease (CD). Fluticasone propionate is a poorly absorbed halogenated corticosteroid with extensive first pass metabolism. In a pilot study in 12 patients with active CD (six male, six female, age 23–64 years), we assessed the effect of three weeks’ treatment with fluticasone propionate – 20 mg daily by mouth. Patients were assessed on clinical criteria, by CDAI, and by Indium leucocyte techniques, measuring scan density and leucocyte excretion from whole body counts. All patients completed the study with no side effects. All parameters improved over the three weeks. Indium scans were positive in all 12 patients before treatment and normal in seven. Leucocyte excretion fell from 28 (20%) injected dose to 13-2 (7%) (p<0.05), CDAI fell from 193 (84) to 130 (43) (p<0.01). Short synacthen tests showed no pituitary-adrenal axis depression.

In this open study, fluticasone propionate seemed effective in the treatment of mild and moderately active small intestinal and colonic CD, meriting further assessment in randomised controlled trials.

Oral cyclosporin and renal function in Crohn’s disease

A J L OBO, I D JUBY, P N FOSTER, J ROTHWELL, A H SMITH, AND A R AXON (Gastroenterology Unit and Dept of Nuclear Medicine, General Infirmary, Leeds) Twenty one patients with Crohn’s disease were treated with oral cyclosporin to determine its effect on renal function in patients with Crohn’s disease. Cyclosporin was given orally (5 mg/kg reduced by 1 mg/kg every two months) until a maintenance dose of 2 mg/kg was reached. Renal function was assessed by measurement of serum creatinine, blood pressure, and urine analysis. In addition, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured, using radioisotope techniques, before treatment and after six weeks and six months. The GFR (median at entry 122 ml/min) fell significantly after six weeks’ treatment with cyclosporin (median 101 ml/min; p=0.001). This was associated with a fall in the ERPF (median ERPF at entry=491 ml/min; median six week ERPF=395 ml/min; p<0.001). After 24 weeks’ treatment and after reduction of the dose of cyclosporin, there has been not a rise in GFR (median 109 ml/min; n=11) or ERPF (median 347 ml/min; n=11). Over this period there was a significant rise in serum creatinine which fell to baseline values after 24 weeks (n=8). Side effects necessitating withdrawal of the drug were seen in six patients.

Does antituberculous chemotherapy for Crohn’s disease provide longterm benefit? A five year follow up study

J L SHAEFFER AND L A TURNBERG (Dept of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) In 1984 we reported that a trial of rifampicin and ethambuton failed to benefit 26 patients with Crohn’s disease. The patients (14 male, 12 female), median age 35 years (range 22–50) were randomised in a double blind placebo controlled crossover design trial over two years. The mean (SD) Crohn’s disease activity index (CDAI) was 210 (37) at trial start. 156 (15) after 12 months placebo, and 183 (20) after active therapy (NS). Fourteen patients completed and 12 were withdrawn before the end of the trial because of surgery (in four), adverse effects (in two), or poor compliance (in four). In the follow up period three patients in the completed group have required surgical resection, as have four patients in the withdrawal group. Corticosteroids or azathioprine or both, were used in 10 of the completed group and eight of the withdrawal group. One patient in each group developed a cancer – one rectal, one anal. There have been no deaths. Three patients in each group remained well throughout. These results are comparable to the overall surgical resection rate of our unit of 45% and a steroid/immunosuppression prevalence of 70%; over a five year period.

Despite experimental evidence implicating mycobacteria, there was no apparent short or longterm benefit after using two standard antituberculous drugs in patients with Crohn’s disease.

Colour Doppler imaging in inflammatory bowel disease

S H LEE AND W R LEES (Dept of Imaging, Middlesex Hospital, London) Twelve patients with known or suspected inflammatory bowel disease were studied with conventional ultrasound together with colour Doppler imaging (CDI). The object was to determine disease extent and activity from the presence of both bowel wall thickening and, more importantly, by an increase in local blood flow using CDI.

The patients were assessed without knowledge of their clinical findings or diagnosis. Six patients had clinical and biochemical evidence of active disease, three with Crohn’s disease, two with previously undiagnosed terminal ileitis, and one with ulcerative colitis. Ultrasonography showed bowel wall thickening in all patients, but only five had an increase in bowel wall blood flow. In the one patient with terminal ileitis without significantly increased blood flow, the clinical evidence for disease activity was weak. In six patients with Crohn’s disease, without evidence of active disease, ultrasound showed bowel wall thickening in
four, with negative findings on CDI in all six.

It is accepted that clinical parameters alone give a poor measure of disease activity. Ultrasound scan of bowel wall thickening is useful but combined with the presence of abnormal blood flow in and around the bowel wall may be a better indicator of activity.

**Microscopic activity in ulcerative colitis – what does it mean?**

S A Riley, S Duit, and M E Herd (Dept of Medicine, Hope Hospital, Salford and Dept of Histopathology, Bury General Hospital, Manchester) Histological evidence of inflammation is not uncommon in patients with quiescent colitis. We have therefore studied the relation between microscopic inflammation and colitis relapse.

Eighty two patients (44 male, 38 female; aged 21–78 years) with colitis in clinical and sigmoidoscopic remission underwent rectal biopsy. Sections were graded independently by two histopathologists. A chronic inflammatory cell infiltrate of varying severity was present in all biopsy specimens. In addition, 32% had evidence of acute activity (acute inflammatory cell infiltrate 28%, crypt abscesses 11%, mucin depleton 22%).

Patients received oral SSZ or 5-ASA as sole maintenance treatment. During 12 months follow up, 27 patients (33%) relapsed (mean interval 18 weeks, range 3–44).

Indices of acute inflammation on entry were associated with significantly higher relapse rates. The presence of an acute cell infiltrate increased the rate to 52%, crypt abscesses to 78%, and mucin depletion to 56%. In the absence of these features rates fell to 25, 27, and 26% respectively. The severity of the chronic inflammatory cell infiltrate, however, was unrelated to the frequency of relapse.

Microscopic evidence of acute inflammation in patients with quiescent colitis is associated with an increased risk of colitis relapse. These patients may benefit from additional maintenance treatment.

**Short term response to treatment in microscopic colitis**

R A Fasoli and D P Jewell (Gastroenterology Dept, John Radcliffe Hospital, Oxford) Microscopic colitis (MC) is characterised by chronic watery diarrhoea, normal endoscopic appearances but with histological inflammation. Response to treatment has been variously reported. The short term response to treatment is reported in 16 patients (four male, 12 female) with a mean age 57 years (range 23–86), in whom MC was diagnosed. The median duration of diarrhoea was 10·5 months (range 2–86). The median follow up after diagnosis was five months (range 2–25). Two patients achieved spontaneous remission (in one case proved histologically). Three responded to a combined regimen of sulphamalazine and prednisolone. Eleven patients were initially treated with either sulphamalazine or mesalazine above. Seven (63%) experienced clinical remission (in three confirmed histologically). Of the four patients who failed to respond, two gained improvement on systemic corticosteroids (one with proved histological remission). One responded to a combination of disodiumcromoglicate and exclusion diet, whereas one failed to have benefit from steroids, metronidazole, or dietary management. There was no correlation between therapeutic response and histological features.

Thus, most patients with MC respond to 5-aminosalicylic acid, but corticosteroids may also be required. Spontaneous remissions may occur.

**Increased leukotriene B4 release from ileal pouch mucosa in ulcerative colitis compared with familial adenomatous polyposis**

D J Geriner, M V Madden, G Deucci, D S Rampton, E Dyk, R J Nicholls, and J E Lennard-Jones (St Mark’s and The London Hospitals, and The William Harvey Research Institute, St Bartholomew’s Medical College, London) Pouchitis in ileal pouch occurs in ulcerative colitis (UC) but not in familial adenomatous polyposis (FAP). To see if differences in eicosanoid metabolism might explain this observation, we studied the release of leukotriene B4 (LTB4) and prostaglandin E2 (PGE2) from mucosal biopsy specimens of sigmoidoscopically uninfammed ileocaecal pouches in continuity with small intestine (UC=10, FAP=six). In six further UC patients, biopsy specimens were taken from a defunctioned pouch and loop ileostomy. Specimens were incubated in Tyrod’s solution at 37°C for 20 minutes with arachidonic acid (10 µg/ml), and eicosanoid release was measured by radioimmunoassay.

LTB4 release was greater from functioning pouches in UC (mean (SEM) 70 (11) ng/g wet weight/20 min) than FAP (32 (8), p=0·02). A trend towards increased PGE2 release did not reach statistical significance (UC 320 (66) ng/g ww/20 min, FAP 202 (66), p=0·36). In UC, defunctioned pouches produced similar results (LTB4 69 (10), PGE2 355 (101)) to functioning pouches. Eicosanoid release from ileostomy biopsy specimens (LTB4 57 (10), PGE2 279 (85)) resembled that from pouches.

Enhanced LTB4 release from endoscopically normal functioning pouches, defunctioned pouches, and ileal mucosa proximal to the pouch suggests increased ileal mucosal 5-lipoxygenase activity in patients with UC and may explain their predisposition to pouchitis.

**Lymphoplasmacytoid cell infiltration correlates with histological severity in Crohn’s colitis**

M C Allison, I W Poultier, A P Dhillion, and R E Pounder (Academic Dept of Medicine and Immunology, Royal Free Hospital, London) Double immunofluorescence studies on cryostat sections of colonic mucosa from patients with inflammatory bowel disease have enabled us to identify a population of lamina propria lymphoid cells (LPL) that display a restricted mosaic of the leucocyte common antigen (CD45R), but fail to express characteristic T or B cell surface antigens. Combined indirect immunoperoxidase alkaline phosphatase studies showed that >90% of CD45R+ LPL outside lymphoid follicles co-expressed the plasma cell surface antigen RF6D and CD38. The proportions of LPL expressing CD45R, CD6 (a pan T cell surface determinant) and both antigens were enumerated in normal colonic mucosa (eight patients), and in sections affected by ulcerative colitis (UC – five patients) and Crohn’s colitis (11 patients). The CD45R reagent recognised significantly higher proportions of non-T lymphocytes in UC (median (range) 50% (20–70%)) and Crohn’s colitis (40% (20–74%)) compared with normal mucosa (6% (5–20%)). There was significant correlation between the proportions of CD45R+ non-T cells and histological severity in the Crohn’s colitis sections (r=0·83, p<0·01).

These results suggest that a large propor-
tion of lymphoid cells infiltrating the colonic mucosa in inflammatory bowel disease derived from B cells which have lost the characteristic B cell surface antigens while in the process of differentiating into plasma cells.

Crohn’s disease and pregnancy in north east Scotland: a community study

M HUDSON, G FLETT, T S SINCLAIR, AND N A G MOWAT (GI Unit and Department of Obstetrics, Aberdeen Teaching Hospitals) Little data exists on the relation between Crohn’s disease (CD) and pregnancy. We studied the relation in all 209 women aged 16–45 years with proved CD during 1967–86. Data were derived from the central records department and from a detailed questionnaire to which we have received 130 replies. Of these, 39 had completed their family before the onset of symptoms. Of 91 potentially fertile women, 56 (61.5%) had conceived on 98 occasions. Only seven (7.7%) had involuntary infertility. A total of 69 normal live births (including three premature), 14 spontaneous abortions, eight social terminations, and one still birth were recorded. No congenital abnormalities occurred. Spontaneous abortion was more common in those with active CD at conception, colorectal CD, and those who underwent surgery before conception. Of those with normal live births, 61 were in remission at conception, but six (9.8%) relapsed, five in the puerperium. Of four with active CD at conception, three went into remission.

Fertility in CD is not impaired. The risk of miscarriage is higher if CD is active at conception, or in colorectal CD, and in those who have had surgery for CD.

GASTRODUODENAL POSTERS

Comparison of two provocative tests in patients with non-cardiac chest pain

A ANGGIASAH, T ROKkas, M MCCULLAGH, AND W J OWEN (Dept of Surgery, Guy’s Hospital, London) The aim of this study was to examine retrospectively symptom provocation and oesophageal motility in response to oesophageal acid perfusion (AP) and iv edrophonium (E) tests in patients with non-cardiac chest pain.

A total of 110 such patients were referred to our laboratory and oesophageal motility was studied during baseline manometry (Gaeltec), AP, and iv E (80 μg/kg BW) tests. The occurrence of pain replicating the patient’s typical symptom was regarded as a positive AP test whereas the positive E test was defined as symptom reproduction associated with manometric abnormalities such as increase of peristaltic amplitude to greater than 200 mmHg and duration longer than seven seconds, or repetitive synchronous activity.

Altogether 29 patients (26.4%) had positive AP test whereas 26 (23.6%) patients had positive E test. Eight patients had both tests positive. There were no significant differences between the two tests as far as reproduction of chest pain was concerned. In the group of patients with positive AP test, 12 of 29 (41.3%) showed motility disorder whereas in the E positive test group the percentage was 100% (26 of 26). In the latter group, 14 of the 26 patients showed normal baseline manometry before E test.

In patients with recurrent non-cardiac chest pain, iv E provocative test is as useful as AP test in reproducing chest pain but in conjunction with manometric findings it is superior (p=0.001) in diagnosing oesophageal motility disorders responsible for this symptom.

Objective evaluation of Angelchik anti-reflux prosthesis – seven year results

C S ROBERTSON, D F EVANS, S J LEDINGHAM, D L MORRIS, AND J D HARDCASTLE (Dept of Surgery, University Hospital, Nottingham) The Angelchik antireflux prosthesis (ACP) is widely used throughout the world but there is no published longterm objective evaluation of its performance. We have inserted ACPs in 42 patients with gastro-oesophageal reflux (GOR). Six prosthesis were removed, four for severe dysphagia because of rotation displacement (between one and seven months) and two with thoracic migration causing persistent GOR (14 and 40 months). Thirty six patients were invited for objective assessment with manometry, pH monitoring, and endoscopy. Four patients were lost to follow up, 13 declined further investigations and were symptom-free, leaving 19 who agreed to be studied (median (range) follow up 54 months (20–87)). Only two patients had mild oesophagitis at endoscopy. Manometry showed a median lower oesophageal sphincter pressure of 12 cm H2O (5–16) with a median intra-abdominal sphincter length of 2 cm (1–5). 24 hour pH monitoring was within normal limits in 14

High selector vagotomy: subjective assessment of outcome

The British Society of Gastroenterology

High lessor curve gastric ulcer; results of highly selective vagotomy with ulcer excision in 24 patients

I G MARTIN, D JOHNSTON, R C MACDONALD, W A F MACADAM, AND T R AXON (University Dept of Surgery and Dept of Gastroenterology, The General Infirmary, Leeds and Airedale District General Hospital) The high lessor curve gastric ulcer (HLCGU) has been regarded as a difficult condition to treat. Some viewing it as a different disease from ulcers of the body of the stomach. We considered the HLCGU as a peptic ulcer, treating it as such. Between 1969 and 1989 we have treated 24 patients with HLCGUs by highly selective vagotomy (HSV) with ulcer excision or biopsy; during the same period 85 patients with ulcers of the gastric body were treated by HSV(E).

The median age was 57 years. Four were emergency operations for haemorrhage, the remainder elective. There was one operative death (4%) early in the series but no subsequent ulcer related mortality. One patient developed a gastric adenocarcinoma 16 years after HSV(E) for a HLCGU. Reductions in peak acid output were as great in patients with HLCGU’s as in patients with ulcers of the body (64%, n = 13 v 64-3%, n = 35). Three patients developed recurrent ulceration (RU) after HSV(E) for HLCGU and eight after HSV(E) for ulcers of the gastric body. 12% of 10% NS; RU was unrelated to reductions in acid output. Two RU’s were treated medically, the third requiring B1 PG. Visick grades at the end of follow up were 88%, I + II and 12%. IV, two patients being graded adversely.

Highly selective vagotomy provides an alternative treatment for the high lessor curve gastric ulcer, with good functional results and without an excessive incidence of recurrent ulceration.

Highly selective vagotomy: subjective assessment of outcome
After procedure, evaluate the bile salt in HIERIR with an11.

Hitherto, increased symptoms, I seven lessomatic. Twenty in section, some (71%).

managed successfully. The British Most duodenal ulcer

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ventrally between 1972 and 1988 inclusive. was conducted by means of a detailed postal questionnaire supplemented by telephone or personal interview. Of 590 patients circularised, 464 returned a valid reply (79%). Altogether 332 were men and 132 women (m:f ratio 2.5:1). A total of 74% (342) denied further symptoms after surgery. Some 158 of 222 patients operated on for more than 10 years were asymptomatic (71%), while 184 of 226 operated on for less than 10 years (81%) were asymptomatic. Twenty six per cent admitted to symptoms ranging from occasional dyspepsia to proved recurrence. Of 122 patients with symptoms, 37 (8%) had had a recurrent DU diagnosed since operation or at review, seven had another diagnosis, while 78 are currently being reviewed. When asked to grade their result (and exclude recurrence) 87% of respondents regarded surgery as successful and were graded Visick I or II.

Highly selective vagotomy, with an 87% patient satisfaction rate, should retain its role for chronic or complicated DU disease.

Raised fasting serum gastrin in chronic gastritis is independent of Campylobacter pylori status and duodenal ulceration

J J WYATT, B J RATHBONE, D M GREEN, AND J PRIMROSE (Depts of Pathology and Medicine, St James's University Hospital, and Pathology and Surgery, Leeds General Infirmary, Leeds) To clarify the relation between gastritis, Campylobacter pylori (CP), gastrin secretion, and duodenal ulcer (DU) we studied 50 dyspeptic patients (age median (range) 42 (20–82) years) 21 male, 29 female; 23 with active DU, 27 with normal endoscopy. Six gastric biopsy specimens from each were graded for gastritis and CP density (Gianma stain). In all antil biopsies, G cells stained by immunoperoxidase were counted on an image analyser. Fasting serum gastrin was measured by radioimmunooassay (normal 100 pg/ml).

All 23 DU patients had CP and gastritis. Of the others, 15 had CP gastritis, four CP negative gastritis, and eight were CP negative with entirely normal mucosa. Serum gastrin was undetectable in the eight with normal mucosa and three with gastritis. Serum gastrin was 4–240 pg/ml (median 23 in the other 39; there was no significant difference between DU/non-DU patients with gastritis or between CP positive and negative gastritis. Serum gastrin was >100 pg/ml in three patients, all with CP including one with DU: none had atrophic fundic mucosa. Gastrin cell counts were significantly lower in CP positive patients than those with normal mucosa and decreased significantly with increasing antral atrophic gastritis, independent of CP status.

We conclude that fasting serum gastrin is higher in gastritic patients with or without CP than in patients with normal mucosa, and is similar in patients with CP whether or not they have DU. Despite undetectable fasting serum gastrin in non-gastritic patients, their antral G cell counts are significantly higher than those with gastritis.

Acid inhibition and mucosal protection with a new proton pump inhibitor

J K DANESHMEND, H K SHARMA, N K BHASKAR, A B HAWTHORNE, AND C J HAWKES (Dept of Therapeutics, University Hospital, Nottingham) AG1749 is a novel substituted benzimidazole, with potent antisecretory action in animals. We evaluated acid inhibition and gastric mucosal protection by AG1749 in humans.

Fifteen healthy volunteers took, over 48 hours on four randomised occasions, each of placebo; aspirin 900 mg bd; aspirin 900 mg bd, plus AG1749 30 mg manc. By orogastric intubation, pH of basilar aspirates and washings and microbleeding rates were measured. Ten volunteers underwent endoscopy (Lanza grades).

The basal pH was similar after aspirin or placebo (median 2.37 (interquartile range 1.99–2.52) v 2.75 (2.34–4.15)). AG1749 raised the pH to 6.20 (3.84–7.60), p=0.025 for 30 mg and 7.08 (6.80–7.68), p=0.018 for 60 mg. The pH of gastric washings rose from 2.26 (2.10–2.50) to 5.0 (2.73–6.44), p=0.0052 with 30 mg and 6.89 (4.43–7.05), p=0.007 with 60 mg. Endoscopic injury to the gastric body rose from 0 (0–0.5) to 3.0 (1.5–3.0), p<0.01 with aspirin and was reduced by AG1749 60 mg to 1.0 (0–2.0), p<0.05 compared with aspirin; not significantly different from placebo. Aspirin increased spontaneous bleeding from mean 1.48 (95% confidence interval 0.77–2.82) ul/10 min to 12.01 (6.12–23.58) ul/10 min; it was reduced to 5.06 (2.65–9.66) ul/10 min by AG1749 30 mg (p=0.053) and to 2.25 (1.18–4.29) ul/10 min by AG1749 (p=0.0004).

AG1749 is a potent acid inhibitor which protects human gastric mucosa.

Drug induced recurrent chronic gastric and small bowel ulcers: an x-ray spectroscopy analysis of mucosal biopsies

N ECTORS, K GEBEES, J V VAN ISVELDI, P RUITFERRIS, V DESMET, AND G VANTRAPPEN (Lab Histo & Cytchemistry, Dept Med Res, KU Leven, Belgium) Intrautable jejunal ulceration occurring after peptic ulcer surgery may be due to the surreptitious use of...
A new method of harvesting bile salts from the upper digestive tract

S M SHIMI AND A CUSCRIERI (Dept of Surgery, Ninewells Hospital and Medical School, Dundee, Scotland) Beads made of sep-pak resin immobilised in calcium alginate are loaded into perforated silicon-rubber capsules with steel caps (24x0.63 mm). Each capsule is capable of absorbing 91.6% of 300 µg of bile salts in solution. Altogether 91.5% of the absorbed bile salts can subsequently be recovered.

Five healthy volunteers (four male, one female) mean age 35 years) each swallowed three capsules after an overnight fast. The capsules were attached by thread and suspended to lie (1) 5 cm proximal to the oesophagogastric junction, (2) in the stomach, and (3) in the third part of the duodenum. The position of the capsules was checked by fluoroscopy. A standard meal was consumed and three hours later the capsules were retrieved. Bile salts were eluted from the resin and the extract assayed by dansyl hydrazone derivatisation and high performance liquid chromatography. Mean (SEM) 89.8 µg (31.08) bile salts were recovered from the capsule in the duodenum (range 18.97-177.59); 0.75 µg (0.14) bile salts were recovered from the capsule in the stomach (range 0.41-1.06); and 0.15 µg (0.04) bile salts were recovered from the capsule in the oesophagus (range 0.02-0.22). The pattern of individual bile salts from the three sites was similar for each individual.

Ascorbic acid inhibits the growth and urease activity of Campylobacter pylori

J GOLDB, S JALALI, S VAN ZANHNN, C STOWE, AND R H HUNT (McMaster University, Hamilton, Ontario, Canada) We studied the effect of ascorbic acid on the urease of Campylobacter pylori (CP) by measuring inhibition of ammonia release in buffered urea solution.

Suspensions (10^6 organisms/ml) of 10 strains of CP were made in NaH2PO4 buffered solution containing ascorbic acid in concentrations of 10, 5, 2, and 1 mg/ml. Parallel control suspensions were made without ascorbic acid. Some 25 µl of CP suspension were inoculated into bottles containing 1.5 ml of buffered urea solution and ammonia concentrations were measured after 30 minutes incubation at room temperature using the Berthelot method. The effect of ascorbic acid on growth of CP was studied on buffered peptone agar media and compared with control media without ascorbic acid.

Ammonia concentrations produced by control inocula without ascorbic acid were all >900 µmol/l. The inocula of CP in ascorbic acid showed inhibition of ammonia formation ranging from 92% at concentration of 1 mg/ml to 98% at 10 mg/ml. Minimal inhibitory concentration of ascorbic acid on growth of CP in buffered peptone agar media was 1 mg/l.

We conclude that: (1) Ascorbic acid is a potent inhibitor of CP urease at concentration of 1 mg/ml. (2) Ascorbic acid also inhibits the growth of CP. (3) Ascorbic acid could have a therapeutic role in eradication of CP by inhibiting its growth and urease enzyme.

Is there a relation between gastric glycoprotein synthesis and the presence of Campylobacter pylori?

V POXON, M WINSLET, K WHEATLEY, P DYKES, AND M R B KEIGHLEY (Dept of Surgery and Medicine, The General and Queen Elizabeth Hospitals, Birmingham) Campylobacter pylori (CP) has an important but ill defined role in peptic ulcer pathogenesis. Its presence is related to a breakdown of the normal mucous barrier by acid, pepsin, and bile. It is unclear if this is associated with reduced gastric mucus production. Glucosamine synthetase (GS) is a rate-limiting enzyme in glycoprotein synthesis, a mucus precursor. This study assessed the association between GS activity and the presence of CP in controls (n=13), patients with non-specific gastritis (NSG=19), gastritis and NSAID's (G+NSAID=nine), gastric ulcer (GU=six), and duodenal ulcer (DU=11).

In the absence of CP, mucous production is reduced in patients with DU compared with controls and those with NSG. but when CP is present, mucous production in DU is increased compared with NSG.

This study suggests that CP is associated with an increased mucus production in patients with NSG and DU but not those with GU. The separation of cause and effect and mechanism of this phenomenon are at present unclear.

Study of the reservoir function of jejunal pouch reconstruction after total gastrectomy

M R GRAY, M O DRISSOULI, M CRITCHLEY, S SAGAR, AND A N KINGSNORTH (Dept of Surgery and Nuclear Medicine, Royal Liverpool Hospital, Liverpool) Postgastrectomy symptoms such as dumping and diarrhoea can be attributed to rapid "gastric emptying". The construction of a pouch from a loop of jejunum (JPR) after total gastricxotomy (TG) is designed to replace the reservoir effect of the stomach. This study examines the function of the JPR in delaying entry of food into the small intestine (SI).

A small volume of a high viscosity meal of "Tc" labelled bran porridge was administered to normal controls (n=seven) and to patients with JPR (n=13) or straight oesophagojejunostomy with Roux-en-Y jejunal loop after TG (n=13).

During ingestion and for 90 minutes afterwards images of the abdomen were acquired on a gamma camera computer system. The percentage of the meal having entered the SI was calculated by subtracting that remaining in the stomach or JPR region from 100%.

Mean values for percentage of meal entering the SI at 15, 45, and 90 minutes respectively were 7, 52, and 80% in the controls. In the JPR patients values were 9, 33, and 58% and in the non-JPR patients values were 62, 76, and 88% respectively.
Salivary epidermal growth factor deficiency in rheumatoid disease: influence of sicca syndrome

S M KELLY, J CHAMPION, AND J O HUNTER (Dept of Gastroenterology, Addenbrooke’s Hospital, Cambridge) Salivary epidermal growth factor (EGF) promotes ulcer healing and contributes to gastric mucosal integrity. EGF deficiency has been reported in patients with rheumatoid disease and may predispose to ulceration. This study determined the contribution of associated salivary gland disease to this reduced output.

Basal unstimulated saliva was collected for 15 minutes from normal subjects (N, n=20) and patients with rheumatoid arthritis (RA, n=20), rheumatoid arthritis with sicca syndrome (RASS, n=nine), and primary sicca syndrome (PSS, n=five). The EGF concentration was determined by radioimmunossay. The Mann-Whitney U test was used for statistical comparison of results, which are expressed as the median (range).

Salivary EGF concentration was reduced in RA (1-32 ng/ml (1-0-4-0), p=e<0-01), RASS (1-35 ng/ml (0-46-2-7), p=e<0-01), and PSS (1-6 ng/ml (1-2-2-45), p=e<0-001) compared with N (3-0 ng/ml (1-45-10)). Salivary volume was profoundly decreased in RASS (1-2 ml/15 min (0-8-2-2), p=e<0-001) and PSS (0-7 ml/15 min (0-2-1-2), p=e<0-001) compared with N (5-7 ml/15 min (2-6-9-4)) but not in RA (4-1 ml/15 min (1-8-9-15), p=n). EGF output was therefore more depressed in RASS and PSS patients than with RA alone.

These results suggest that associated salivary disease is the major contribution to EGF deficiency in rheumatoid patients. It is therefore possible that patients with sicca syndrome form a subgroup in rheumatoid disease more susceptible to gastric injury.

Relation between severity and extent of precancerous gastric lesions in a precancerous condition

W S SAVAGE, C CORISHLEY, C CAYGILL, M HILL, J S KIRKHAM, M COOK, AND J C NORTHFIELD (Norman Tanner Gastroenterology Unit, St George’s Hospital and Medical School, London) Widespread dysplasia is present in early gastric cancer, suggesting a possible relation between severity and extent of dysplastic change. Our aim was to check on the existence of such a relation in a precancerous condition. A total of 87 subjects who had had gastric surgery for benign peptic ulcer >20 years ago underwent endoscopy. Biopsy specimens (n=12) were graded for severity of dysplasia and intestinal metaplasia as indicators of cancer risk. Severity of dysplasia correlated with its extent (r,=+0.50, p<0.001); similarly severity of intestinal metaplasia correlated with its extent (r,=+0.60, p<0.001) and with severity of dysplasia (r,=+0.31, p<0.005). Moderate and severe dysplasia were more frequent around the stoma than elsewhere (p<0.01).

We conclude that there is a relation between the severity and extent of precancerous lesions, suggesting a widespread mucosal instability in patients with dysplasia; and that the workload in screening for gastric precancer can be substantially reduced by assessing severity of dysplasia in six biopsy specimens from the stoma only.

Computerised personal audit for the gastroenterologist 14X8 cm

M DEAKIN AND J B ELDER (North Staffordshire Royal Infirmary, Stoke on Trent) Personal audit is now obligatory for all clinicians. To carry a log book is often impracticable, yet if filled in retrospectively, often from scraps of paper kept in a white coat pocket, can be inaccurate. As a solution to this problem a pocket computer data base has been evaluated over six months.

The computer chosen was a Psion Organizer XP, storing data on a 64K data pack. Using this system individual patient records can be subdivided into up to 16 subsections (fields) and each individual record can be up to 254 characters long.

Over six months, 233 mainly gastrointestinal operations were personally documented under the field headings - Name, Number, Date of birth, Diagnosis, Operation, Op date, Assistant, Op Note and Complications. The median length of each record was 128 characters (range 80-158) taking 1.5 to 2 minutes to enter. The capacitance was 500 records per 64K data pack. Searching the entire data base takes less than two seconds, but for further manipulation and longterm storage the completed records have been transferred onto a desk top computer by data link.

The main disadvantage of the system is cost — approximately £270 for the complete system, but it has the advantage of being compact, portable, and allows complete prospective case analysis and accurate evaluation of training.

Active v quiescent duodenal ulcer: gastric secretion remains unchanged

M DEAKIN AND J G WILLIAMS (North Staffordshire Royal Infirmary and Postgraduate Medical School, Swans) There are conflicting reports concerning gastric acid secretion in patients with active compared with quiescent duodenal ulcers.

We have studied evening and overnight intragastric pH (1800-0730) and nocturnal (0030-0730) acid, volume and pepsin outputs in 32 patients with active ulcers and compared the results with a group of 10 patients with duodenal ulcers in remission using a standardised aspiration technique.

The results were — (median, range), active v quiescent ulcers) — acid output (mmol), 23-6 (2-1-207-5) v 17-1 (0-0-77-5); pepsin output (IU) 27-2 (2-3-134-4) v 25-7 (0-0-109-7); pepsin concentration (IU/L) 80-0 (23-0-271-0) v 110-0 (0-0-146-0); volume output (ml) 371 (59-1590) v 306-0 (32-792); and nocturnal pH 1-57 (1-16-2-8) v 1-38 (1-25-8-16).

There were no significant differences between the two groups for nocturnal gastric secretion or intragastric pH at any time point (Mann Whitney).

These data support the hypothesis that the main problem in duodenal ulcer disease is loss of mucosal resistance to aggressive factors for a period of time and not that gastric secretion changes. Further advance in the understanding of duodenal ulcer disease is likely to come from investigation of mucosal factors rather than gastric secretion.

Decreased leukotriene C4 formation after eradication of Campylobacter pylori in gastritis by colloidal bismuth subcitrate

A AHMED, D ARVANITIDIS, J HOLTON, M HORSEY, P R SALMON, AND I R HOULT (Depts of Gastroenterology, Microbiology, and Surgery, The Middlesex Hospital, London) Pronflammatory peptido-leucotrienes have been shown to be increased in Campylobacter pylori (CP) associated
gastritis. We have measured leukotriene C₄ (LTC₄) formation by RIA in antral biopsy specimens taken from 28 dyspeptic patients and incubated at 37°C, both in the absence (basal) and in the presence (stimulated) of calcium ionophore. Ten patients showed normal antral histology with no evidence of CP. The remaining 18 patients exhibited histological gastritis and were CP positive as assessed by histology and CP test. Twelve of these 18 patients received four weeks colloidal bismuth (CBS) treatment before re-endoscopy. Basal release of LTC₄ in normal, abnormal, and CBS-treated mucosa were similar (pg/mg w/w/20 min; mean (SEM): 61.9 (10.8); 71.9 (8.7); 56.6 (7.2) respectively). Mean stimulated LTC₄ value was significantly higher in CP positive mucosa than in CP negative mucosa (124.2 (15.7) vs 66.0 (11.0); p<0.02). After eradication of CP by CBS, there was a decrease in gastritis and a significant reduction in ionophore-mediated LTC₄ formation (68.5 (9.3)) compared with before treatment (p<0.02).

Presence of CP is associated with increased capacity to generate LTC₄ which may have pathological significance; likewise CBS’s benefit may be due to reduced LTC₄ formation.

Mucosal defence in Campylobacter pylori patients with duodenal ulcer and gastritis – effect of De-Nol

P M GOGGIN, J MARRERO, S H SAVERYMUTTU, C C W YU, C M CORBISHELY, AND T C NORTHFIELD (Dept of Medicine, St George’s Hospital Medical School, London) We have shown that human gastric mucosa has a very hydrophobic surface, repelling aqueous solutions including acid; and that hydrophobicity is reduced in duodenal ulcer (DU) and Campylobacter pylori (CP) gastritis. Our aim was to determine the effect on CA of clearance of CP with tiotiapumide dicitrato bismuthate (De-Nol).

Patients with (n=16) or without (n=19) DU found to have antral CP were entered into an investigator blind trial of ranitidine 150 mg bd 1/12 v De-Nol tab 2 bd 1/12 v De-Nol tab 2bd 1/12 + amoxicillin 500 mg bd 2/52. Antral biopsy specimens were taken for histology, quick uncrase test, and measurement of CA using a goniometer, at presentation and at the end of one month’s treatment. CA (mean (SEM)) was reduced in CP positive gastritis (54.4 (1), p<0.001) and CP positive duodenal ulcer (53.9 (9), p<0.001) v CP negative controls without gastric pathology (68.1 (7), n=30). CA was unchanged after treatment with ranitidine (53.5 (8) v 55.9 (1-9) NS), but increased after treatment with De-Nol tab (54.3 (12) to 64.2 (2.7), p<0.02, n=10) and De-Nol tab + amoxicillin (54 (1-5) to 63-6 (2-4), p<0.002, n=11). Clearance of CP (15 of 20 De-Nol, 0 of 9 ranitidine) was associated with an increase in CA (54-4 (1-4) to 66-4 (1-8), p<0.0001).

We conclude that CP infection is associated with a reduction in gastric mucosal hydrophobicity and that clearance of CP is associated with a reversal of this abnormality. This may provide an important clue to the mechanism whereby CP infection impairs mucosal defence against acid/peptic digestion.

Effect of bile salts on growth of Campylobacter pylori

J GOLDFI, S JAIALL, S VANZANTEN, AND R H HUNT (McMaster University, Hamilton, Ontario, Canada) Campylobacter pylori (CP) has been implicated in peptic ulcer disease and gastritis. Various treatment regimens have failed to eradicate it. Patients with bile reflux gastritis have paucity of CP, suggesting that bile may have inhibitory effect on CP. We studied the effect of bile salts, ursodeoxycholic acid and chenodeoxycholic acid, on growth of 32 clinical isolates of CP.

Suspensions of CP (10⁶ organisms/ml) in buffered peptone water were inoculated onto plates of buffered peptone agar containing ursodeoxycholic acid or chenodeoxycholic acid in concentrations of 10, 25, 50, 100, 250, 500, and 1000 pg/ml. Parallel suspensions were inoculated on control media without bile salts.

Ursodeoxycholic acid inhibited the growth of CP in concentrations of 500 µg/ml or more and chenodeoxycholic acid in concentrations of 250 µg/ml or more. Growth was observed in all control media without bile salts.

We conclude that: (1) Bile salts have an inhibitory effect on the growth of CP. (2) Minimal inhibitory concentration of chenodeoxycholic acid is 250 µg/ml and 500 µg/ml with ursodeoxycholic acid. (3) Bile salts could have an important treatment role in eradication of CP, either alone or in conjunction with other existing agents.

CA 72-4 and gastric cancer

D J BYRNE, M C K BROWNING, M P HOLLEY, AND A CUSCHIERI (Depts of Surgery, Biochemical Medicine, and Pathology, Ninewells Hospital and Medical School, Dundee) At present there is no tumour marker that significantly predicts disease activity and survival in gastric cancer. A carbohydrate antigen, TAG-72, which fails to react to non-epithelial malignancies, is present in the serum of patients with gastrointestinal tumours.

In the present study, serum TAG-72, CA 19-9, and CEA were assayed, using specific monoclonal antibodies, in 30 consecutive patients with gastric cancer before surgery and in 30 age matched controls. The results of the assays, which were performed blind, were correlated with disease stage and survival after surgery during a follow up period of up to 20 months.

The CEA and CA 19-9 data were non-discriminative and did not improve the predictive value of TAG-72. These findings indicate that TAG-72 is a useful monitor of disease activity, stage, and survival in patients with gastric cancer but confirmation by larger studies with longer follow up is necessary.

Simultaneous evaluation of the role of intragastric bile acids, sodium, and nitrosation in gastric carcinogenesis

R S SAVAIG, C CAGGILL, A R COOK, S LEACH, S DUNCAN, R SPYCHAL, C WALTERS, M HILL, C CORBISHLEY, M COOK, J S KIRKHAM, AND T C NORTHFIELD (Norman Tanner Gastroenterology Unit, St George’s Hospital and Medical School, London) The involvement of intragastric bile acids, sodium, and nitrosation in gastric carcinogenesis remains controversial. We have examined their role in a single study, relating them to gastric dysplasia after gastric surgery.

Altogether 87 subjects who had had gastric surgery 20 years ago underwent endoscopy. Gastric juice was collected and gastric biopsy specimens (n=12) were taken for dysplasia grading. BII subjects (n=52) had a significantly higher frequency of dysplasia (85%, p<0.01) than those with other gastric operations (BI or vagotomy and drainage n=35, 51%). The latter group had lower values than BII subjects for intragastric pH (mean (SEM) 7.7 (1), p<0.002); nitrite (59 (8) µmol, p<0.002); nitrosating bacteria (2.7 (0.3), log bacterial count p<0.025); percentage conversion to nitrite (19 (3%), p<0.02); and bile acids (6856 (993) µmol, p<0.004). The intragastric sodium concentration correlated with that of bile acids (r=+0.50, p<0.001).
and with the grade of dysplasia (r=0.25, p<0.05).
These findings are consistent with all three factors having a role in gastric carcinogenesis.

Tolerance during eight days of high dose H2 blockade: placebo controlled studies of 24 hour acidity and gastrin

J T L SMITH, C J GAVEY, C U NWOKOLO, AND R E POUNDER (Academic Dept of Medicine, Royal Free Hospital School of Medicine, London) Simultaneous 24 hour intragastric acidity and plasma gastrin concentrations were measured in 24 healthy subjects, before (D0) and on day 1 (D1) and D8 of dosing with placebo (n=eight), ranitidine 300 mg qds (n=eight), and ranitidine 1200 mg om (n=eight). Triplicate placebo studies showed no significant differences in either median 24 hour integrated acidity (861, 885, and 1028 mmol/h/l; 0.3<p<0.05) or plasma gastrin concentration (196, 209, and 198 pmol/l; 0.95<p<0.08).

Compared with D0, there was a significant fall in the 24 hour integrated acidity on D1 of dosing with ranitidine 300 mg qds (p<0.01) but a significant return of acidity on D8 (791, 92, and 179 mmol/h/l; D1 v D8 p<0.01). Compared with D0, the 24 hour integrated plasma gastrin concentrations were significantly raised on D1 and D8 (152, 403 and 407 pmol/l; p<0.01).

Compared with D0, there was a significant fall in 24 hour integrated acidity on D1 of ranitidine 1200 mg om (p<0.01) with a significant return of acidity on D8 (806, 226, and 492 mmol/h/l; D1 v D8 p<0.01). Compared with D0, 24 hour integrated plasma gastrin concentrations on D1 and D8 were significantly raised (187, 341, and 440 pmol/h/l; p<0.01).

We conclude that tolerance to high dose H2 blockade occurs by day eight of dosing and it could be induced by the observed rise of plasma gastrin concentration.

Tolerance during 29 days of conventional dosing with cimetidine, nizatidine, famotidine, or ranitidine

C U NWOKOLO, C J GAVEY, J T L SMITH, A SAWYERR, AND R E POUNDER (Academic Dept of Medicine, Royal Free Hospital School of Medicine, London) In a series of 192 24 hour studies, six groups of eight healthy subjects were dosed for 29 days with either cimetidine (800 mg no cel), nizatidine (300 mg no cel), famotidine (40 mg no cel), or ranitidine (300 mg no cel, 150 mg bd, or 150 mg no cel). The 24 hour intragastric acidity and plasma gastrin concentration were measured before dosing (day 0) and on days 1, 15, and 29. Integrated acidity and gastrin were calculated as the area under the relevant time-concentration curves.

There was a progressive return of intragastric acidity and a persisting increase in plasma gastrin during dosing with all the H2 blocker regimens. The percentage residual nocturnal acidity values compared with day 0 (A=day 1, B=day 15, C=day 29) were: cimetidine A=3%, B=33%*, C=25%; nizatidine A=3%, B=81%, C=12%*; famotidine A=5%, B=15%, C=32%; ranitidine (300 mg no cel) A=5%, B=12%, C=15%; ranitidine (150 mg bd) A=11%, B=29%, C=48%; ranitidine (150 mg no cel) A=16%, B=32%, C=31%; (p<0.05)*; <0.01** (Wilecox's signed-rank test) compared with day 1.

We conclude that the persisting hypergastrinemia is inappropriate for the returning intragastric acidity, and it may be responsible for 'tolerance' to H2 blockade.

Intravenous pentagastrin can overcome H2 blockade in man: a possible mechanism for tolerance

C U NWOKOLO, J T L SMITH, A SAWYERR, AND R E POUNDER (Academic Dept of Medicine, Royal Free Hospital School of Medicine, London) In a double blind study of Latin square design, we dosed 12 healthy men with a combination of ranitidine 300 mg or placebo (at 0800 hour) and intravenous pentagastrin (0-6 mg/kg/h) or normal saline (0700-1800 hours). Hourly intragastric acidity and plasma gastrin concentrations were measured during the four combinations: A=ranitidine/pentagastrin; B=placebo/pentagastrin; C=ranitidine/saline; D=placebo/saline.

Our results (acidity=median 10 hour integrated acidity; gastrin=median 10 hour integrated gastrin) show that: compared with regimen D, regimen B raised acidity (315 to 615 mmol/h/l, p<0.001) and lowered gastrin (86 to 55 pmol/l, p<0.001), but regimen C lowered acidity (315 to 67 mmol/l, p<0.001) and raised gastrin (86 to 209 pmol/l, p<0.001). Compared with regimen C, regimen A returned acidity towards normal (67 to 293 mmol/l, p<0.001) and lowered gastrin (209 to 135 pmol/l, p<0.001).

We conclude that a continuous pentagastrin infusion can overcome H2 blockade and return intragastric acidity towards normal. Hypergastrinemia observed during continued dosing with H2 blockers may be the mechanism for the development of tolerance.

Effect of smoking on pharmacokinetics of famotidine and intragastric pH

I C BAAK, S GANESHI, J B M J JANSEN, AND C H W LAMERS (Dept of Gastroenterology, University Hospital, Leiden, The Netherlands) Previous studies have shown a correlation between smoking, peptic ulcers, and slower healing with H2 receptor antagonists. We studied the effect of smoking on pharmacokinetics of the H2 receptor antagonist famotidine, and intragastric pH (IPH) in 12 healthy habitual smokers (five male, seven female; median age 22 years) and eight non-smokers (four male, four female; median age 24 years). Famotidine (40 mg) or placebo was administered 15 minutes after breakfast in a randomised, double blind crossover trial. Smokers smoked one cigarette every 30 minutes, starting one hour before (A), or two hours after (B) drug administration. In study period C they did not smoke. Blood samples for famotidine were taken every 30 minutes for eight hours after drug administration. Median 24 hour IPH values were measured with an ambulatory pH recorder.

Famotidine (40 mg) raised median 24 hour IPH in non-smokers and smokers in all study periods (medians (interquartile ranges): non-smokers: 1.50 (1.15-1.80) to 3.25 (2.55-3.90), p<0.01; smokers A: 1.35 (1.12-1.75) to 2.55 (2.12-4.22), B: 1.55 (1.18-1.88) to 2.45 (2.25-3.65), C: 1.40 (1.10-1.60) to 2.45 (2.05-3.22), placebo and famotidine (40 mg), respectively (p<0.005). Smoking habits (A, B, C) did not significantly influence 24 hour IPH for both placebo and famotidine days within smokers when compared with non-smokers. Famotidine values were detectable earlier in plasma from non-smokers than from smokers (p<0.05), but all other pharmacokinetic parameters (maximum plasma concentration, time to peak concentration, area under the time-concentration curve (eight hours)) showed no significant difference in the various experiments.

We conclude that oral famotidine (40 mg) raised 24 hour intragastric pH equally in non-smokers and smokers (regardless of whether they smoked or not), although absorption of famotidine was delayed in all experiments in smokers. All other pharmacokinetic parameters were not significantly different.
Natural killer cell activity in patients with neuroendocrine tumours of the gastrointestinal tract

M N Aparicio-Páges, H W Verspaget, A S Pisa, J B M Jansen, and C B W Lamers (Dept of Gastroenterology, University Hospital, Leiden, The Netherlands) Natural killer (NK) cells play an important role in the immune surveillance of tumours. There is increasing evidence that hormones and neuropeptides can modulate the immune response in vitro. We studied peripheral blood NK cell activity and the in vitro effect of recombinant gamma-interferon (γ-IFN), of 17 patients with gastrointestinal neuroendocrine tumours (11 gastrinoma, one VIPoma, two somatostatinoma, one ileal carcinoid, and two patients with non-functioning pancreatic endocrine tumour) and 23 healthy controls. Peripheral blood NK cell activity was evaluated against the erythroblastleukaemia K-562 cell line in a chromium°release assay at an effector: target ratio of 50:1. The results are expressed in % cytotoxicity and evaluated by the Wilcoxon rank-sum test.

Natural killer cell activity of patients with gastrinoma was similar to that of the controls (63 (4) v 64 (3)). Patients with neuroendocrine tumours without hypergastrinemia showed a decreased NK cell activity compared with the patients with gastrinoma and the controls (44 (6) v 63 (4) and 64 (3), both p<0.05). This impairment was not related to the presence of hepatic metastases in these patients. Follow up studies in seven patients showed NK cell activities not to vary with stable disease, to decrease with progressive disease, and to increase with regression of the disease. The γ-IFN stimulated the cytotoxicity both in patients and controls, but it remained significantly lower in patients without hypergastrinemia than in the other two groups (53 (6) v 71 (2) and 71 (2), p<0.05).

We conclude that NK cell activity is suppressed in patients with neuroendocrine tumours that produce other hormones than gastrin. Thus the excessive gastrin production in vivo does not affect NK cell activity in vitro. The impairment of NK cell activity in other patients is not related to the advancement (metastases) of the disease but seems to be related to the disease development.

Omeprazole or ranitidine for two or four weeks in duodenal ulcer patients: effect on healing, symptoms, and ulcer recurrence during intermittent short term treatment

T Lind, U Håglund, H Hernqvist, and a Swedish multicentre study group (Dept of Surgery, Sahlgrens Hospital, Gothenburg; Dept of Surgery, Akademiska sjukhuset, Uppsala, Hässle Mölndal, Sweden) Omeprazole, 20 mg om (OME) and ranitidine, 300 mg hs (RAN) for two or four weeks were compared in duodenal ulcer (DU) patients.

Duodenal ulcer patients (n=325) were randomised to: OME two weeks+placebo two weeks (OME2); OME four weeks (OME4); RAN two weeks+placebo two weeks (RAN2); or RAN four weeks (RAN4). Patients with unhealed ulcer or evident duodenitis were considered as unhealed. Patients with endoscopic ulcer relapse during a 12 month follow up received identical double blind treatment as previously (maximally three additional courses).

Two week healing rates were significantly higher on OME (70%) compared with RAN (54%; p=0.005), and more patients were symptom free (p=0.001). Significantly more patients were free of daytime pain after four weeks on OME4 (90%) than RAN4 (77%; p=0.03). OME2 did not differ significantly from RAN4 in healing, symptoms, or ulcer recurrences and was inferior to OME4 only in healing and time to first relapse.

We conclude that OME heals DU faster and relieves symptoms better than RAN. Ulcer healing initiated by a two week course was inferior to a four week course, and thus intermittent treatment with OME4 seems to be best in DU patients.

Late follow up of patients with peptic ulcer haemorrhage

P A O’Keeffe, J A Loizou, D Grigg, K Mathewson, J S Kirkham, I C Northfield, and S G Bown (University College Hospital, London, and St George’s Hospital, London) Altogether 144 patients with peptic ulcer haemorrhage (PUH) treated between 1984 and 1986 as part of a randomised trial of endoscopic Nd:YAG laser and heater probe (HP) haemostasis were followed up retrospectively: 51 patients (35%) could not be traced. Four well matched patient groups were identified: Nd:YAG laser group (n=25), heater probe group (n=29), control group (n=17), and early surgery (during index admission) group (n=22). Mean follow up was 27, 25, 32, and 33 months respectively. During follow up further PUH occurred in two laser treated patients (8%), three patients treated with the HP (10%), and one patient in the control group (6%); none of the patients in the early surgery group rebled. The corresponding figures for late ulcer related mortality in these groups were 8%, 5%, 6%, and 0% respectively. Dyspeptic symptoms suggestive of recurrent peptic ulceration (not documented by endoscopy) in the six month period preceding the interview, were reported by 24% of patients in the laser group, 14% in the HP group, 34% in the control group, and 20% in the surgery group; 70% of these were taking H2 receptor antagonists.

We conclude that the incidence of late recurrent PUH in all groups is very low, thus the significantly improved outcome with endoscopic laser haemostasis in the acute phase is maintained long term.

Size and pathology of vessel and ulcer in patients with fatal bleeding from duodenal ulcer

A Grandison, A Kalabakas, D Wingate, D Pollock, and P Swain (Academic Unit of Gastroenterology and Dept of Pathology, The London Hospital, London) In order to examine the nature of the vessel and ulcer in patients with fatal duodenal ulcer bleeding, macroscopic necropsy reports as well as blocks and slides from 60 necropsy examinations were studied. In 25 cases (29 vessels) the material could be adequately assessed and measured at histology. Macroscopic examination recorded a protruding vessel in 27 of 60 (45%) and vessel size in 10 large vessels, mean diameter 2.6 (1.8) mm; seven being identified as gastroduodenal artery. Ulcer position was recorded as posterior in 60%, anterosuperior in 15%, circumferential or multiple in 20%, and in 2nd part in 5%. Ulcer size was large, mean diameter 2.4 (1.3), range 0.5–7 cm. Measurements of eroded vessels found at histology showed mean diameter of 0.9 mm, range 0.1–3.45 mm, 19 measured 0.1–1 mm, eight measured 1.5–3.45 mm. In 23 (79%), the eroded artery was external to muscularis propria while in 6 (21%) it was submucosal. Fibrosis indicating chronic ulceration was present in 16 of 25 (64%). Focal pathological change was common in the eroded artery: atherosclerosis in 17 of 29 (59%), intraluminal thrombosis in 17 of 29 (59%), atheroemboli in 14 of 29 (48%), and atheroma in one of 29 (3%).

We conclude that there is a bimodal distribution of arterial size in patients dying of bleeding duodenal ulcer, with most bleeding from small vessels of less than 1 mm while a third bled from large vessels.
compatible with the main gastroduodenal artery or a large feeding branch. Duodenal ulcers with fatal bleeding were predominantly posterior, chronic, deep, and large.

**Acute tolerance to $H_2$ receptor antagonists**

C H WILDER-SMITH, I ERNST, M GIBSON, B ZEYN, E VARGA, S ROHMEL, F HALPER, AND H S MERKI (Gastrointestinal Unit, Inselspital, University of Bern, Switzerland) To study a possible loss of efficacy after repeated $H_2$ receptor antagonist treatment and the role of gastrin in this tolerance, we conducted two randomised, placebo controlled, double blind, crossover trials with oral ranitidine (R) (300 mg hs and 300 mg qds) and sufactidine (S) (300 and 600 mg bds) given seven and 14 days to 20 and 18 fed, healthy subjects, respectively. Twenty four hour gastric acidity was measured on the first and last day using combined glass electrodes. Plasma gastrin was measured at one to two hourly intervals.

Tolerance was seen within one to two weeks of H2 blocker dosing and showed some dose dependence. The rise in acidity was not accompanied by a reduction in gastrin expected from the feedback known for the acute situation.

**Impact of $H_2$ receptor antagonists on treatment of perforated duodenal ulcer: is definitive surgery now obsolete?**

M C MACINTYRE AND A MILLAR (Surgical Review Office, Western General Hospital, Edinburgh) Simple closure remains the most widely practised operation for perforated duodenal ulcer despite the fact that recent controlled trials have shown that closure accompanied by parietal cell vagotomy is as safe and is associated with superior longterm results. The aim of the present study was to assess whether $H_2$ receptor antagonists (H2RA), started at the time of the initial procedure for perforated duodenal ulcer, give a better longterm symptomatic result than simple closure alone or simple closure accompanied by a definitive procedure.

A total of 167 patients with perforated duodenal ulcer have been prospectively followed up for between three and 20 years. Altogether 109 were treated by simple closure alone (group 1) and 58 by simple closure and immediate H2RA (group 2). The groups were comparable in terms of median age, sex, cigarette, and NSAID consumption, and previous peptic ulcer complications.

Symptomatic results were better in group 2 (2-4% of patients had epigastric pain daily or most days as compared to 7-5% in group 1). The need for subsequent definitive surgery was also less in group 2 (24-1% compared with 36-7%).

We conclude that the immediate addition of H2-RA is associated with a superior long term symptomatic result and a reduced requirement for subsequent definitive duodenal ulcer surgery.

**‘Tolerance’ to $H_2$ receptor antagonists: does it occur and by what mechanism?**

M J ROGERS, J H PRIMROSE, J HOLMFIELD, AND D JOHNSON (University Dept of Surgery, Leeds General Infirmary, Leeds) In order to determine whether tolerance to the acid inhibitory effect of $H_2$ receptor antagonists ($H_2$RA) occurs, the acid inhibitory effect of sufactidine (SUF), a potent, long acting competitive H2-RA, was studied in 12 healthy men in a double blind, randomised, three way crossover study of the effect of placebo, SUF 600 mg nocte, and SUF 600 mg bd given over 15 days. On day 1 and 15 of treatment, each subject’s 24 hour intra-gastric acidity was measured by radiotelemetry and 24 hour gastrin profiles were derived from hourly venous blood samples.

Acid suppression was calculated as the reduction in area under the curve (AUC) of [H+] vs time from that observed on placebo, and 24 hour plasma gastrin (PG) calculated as the AUC of PG versus time.

The 24 hour acid suppression afforded by SUF 600 mg nocte and SUF 600 mg bd did not differ after 15 days treatment, but, even on the first day of treatment, SUF 600 mg nocte inhibited nocturnal acid more potently than SUF 600 mg bd (p<0.005). After 15 days, the acid suppression afforded by both regimens was significantly attenuated (p<0.005); this was paralleled by a rise in 24 hour PG (p<0.001).

We have shown that tolerance to the acid inhibitory effect of H2-RA exists and is of rapid onset. We suggest that tolerance is mediated by the temporally associated rise in 24 hour PG but we cannot exclude the possibility that other mechanisms, such as up regulation of H2 receptors, play a part.

**Cisapride prevents duodenal ulcer relapse**

D D KERRIGAN, M E TAYLOR, N W READ, AND JOHNSON (Dept of Surgery and Sub-Dept of G1 Physiology, Royal Hallamshire Hospital, Sheffield) The ideal drug for the prevention of duodenal ulcer (DU) relapse should be both safe and effective. Cisapride, by promoting antroduodenal coordinated motor activity, may enhance the clearance of acid from the duodenal bulb. It does not affect gastric secretion and is thus free from the potential risks of prolonged gastric hypochlorhydria associated with maintenance H2 blocker treatment.

We present the interim results of a single centre randomised, double blind trial comparing the value of cisapride (10 mg bd) with placebo in preventing the relapse of endoscopically healed DU over a 12 month period. Patients were reviewed every two
months and underwent endoscopy at four month intervals. Of 61 patients entered, 51 (24 cisapride and 27 placebo) have completed the trial. Twelve patients, 10 receiving cisapride, were withdrawn – eight because of protocol violations and four with side effects, namely: vague nausea (placebo), nausea and vomiting (cisapride), deterioration in pre-existing loose bowel habit (cisapride), and irritability-lethargy (cisapride).

Twenty eight DU have relapsed giving a crude cumulative relapse rate of 29% (7 of 24) for cisapride v 78% (21 of 27) for placebo treated patients, ($\chi^2$ test, $p=0.0005$): the time taken for ulcer relapse was similar in each group (median 16 weeks). Even excluding the eight patients withdrawn for non-compliance (seven on cisapride), cisapride was still superior to placebo in the prevention of ulcer relapse (41% cisapride vs 81% placebo; $p<0.01$).

These interim findings suggest that cisapride may be a safe and effective drug for use in the prevention of DU relapse.

Duodenal ulcer recurrence after healing with omeprazole or cimetidine treatment: a multicentre study in the UK

K R SCHILLER, A TR AXTON, D L CARR-LOCKE, R COCKETT, I A DONOVAN, W M EDMONDSTONE, A ELISH, J T GILMORE, R F HARVEY, B D LINAKER, A J MORRIS, C WASTELL, J G WILLIAMS, AND K R W GILTON (St Peter's District General Hospital, Chertsey and Astra Clinical Research Unit, Edinburgh (for the study group only)) In this UK, double blind study, patients with duodenal ulcer (DU) received treatment for up to eight weeks with either omeprazole (20 mg daily) or cimetidine (800 mg nocte) for eight weeks. Successful healing was defined as endoscopy showing that the ulcer had healed. A total of 113 patients were randomly assigned to the control group (75 patients) and 38 to the omeprazole group. Of these patients, 56 (81%) in the omeprazole group and 36 (62%) in the control group were found to have a healed duodenal ulcer by endoscopy. The difference in successful healing rate was statistically significant (chi-squared test, $p<0.01$).

Does smoking impair therapeutic gastric acid inhibition?

M J ROGERS, J N PRIMROSE, J HOLMFIELD, AND D JOHNSTON (University Dept of Surgery, Leeds General Infirmary, Leeds) The nature of the association between smoking and duodenal ulcer (DU) is obscure, but the acid suppression afforded by H2 antagonist (cisapride) is reported to be attenuated by smoking. The aim of this study was to compare the effectiveness of ranitidine (RAN) in smokers and non-smokers with DU.

Forty consecutive patients (mean age 37 years; 33 male, 7 female; 10 non-smokers) referred for operation for DU had 24 hour ambulatory intragastric pH recorded on placebo (PL) and while taking RAN (300 mg at 10 pm). Sleepiness and dietary pattern (and smoking pattern of patients who were smokers) were identical for each recording. Median 24 hour, night time ($0000-0800$) and daytime ($0800-0000$) pH and 24 hour, night time and daytime (H+) (area under (H+) v time curve) were calculated for each recording. Median (quartile) 24 hour pH was 1.5 (1.3-1.7) on PL and 2.6 (2.0-2.7) on RAN in non-smokers, and 1.4 (1.3-1.4) on PL and 2.0 (1.7-2.9) on RAN in smokers (NS, smokers v non-smokers). Median (quartile) 24 hour acid suppression on RAN (reduction in 24 hour (H+) from that on PL) was 53% (32-67) in non-smokers and 60% (37-69) in smokers (NS). RAN suppressed night time (H+) a median 97% (82-99%) in non-smokers and 93% (79-99%) in smokers whereas daytime (H+) was inhibited a median 32% (17-46%) in non-smokers and 31% (3-47%) in smokers (NS).

Cigarette smokers do not significantly alter the therapeutic inhibition of gastric acid afforded by RAN; and thus impaired acid suppression does not underlie the slower healing of duodenal ulcers observed in patients who smoke.

Does healing of oesophagitis depend solely on reducing oesophageal acid exposure?

A P BARLOW, T L NORRIS, AND A WATSON (Dept of Surgery, Royal Lancaster Infirmary, Lancaster) Most patients with oesophagitis have abnormal oesophageal exposure to gastric acid on prolonged pH monitoring. Although antireflux treatment aims to correct this, the relation between healing of oesophagitis and control of acid reflux is poorly understood.

Fifty patients with reflux oesophagitis underwent endoscopy and oesophageal pH monitoring before entering a placebo controlled trial of an H2 receptor antagonist. Studies were repeated on medication at eight week intervals. Fourteen patients subsequently had antireflux surgery.

Oesophagitis healed in 24 patients, improved in 20, and was unchanged in 42.

Interobserver variations on routine flexible oesophagoscopy

M MCCULLAGH AND W J OWEN (Dept of Surgery, Lewisham and Guy's Hospitals, London) Flexible endoscopy is often the first step in the investigation of suspected gastro-oesophageal reflux (GOR). The criteria used to diagnose mucosal and anatomical abnormalities are well described (Savary), although there is no information on the degree of interobserver variation.

To assess (a) the variability of observations in an upper gastro-intestinal endoscopy (OGD) and (b) the correlation of histology with naked eye assessment, two trained endoscopists examined 40 consecutive patients referred for routine OGD and
independently recorded the level of (1) the squamocolumnar junction (SCJ), (2) the diaphragm, (3) the oesophagogastric junction (OGJ), and (4) the grade of inflammation present (standard Savary classification). Biopsy specimens were taken at random 5–8 cm above the OGJ.

The results regarding the SCJ, the OGJ, and the grade of inflammation, were in exact agreement in 63%, 74%, and 76% respectively (p=NS Mann Whitney). There was wide disparity in observations made regarding the level of the diaphragm (up to 7 cm, p=0.002). In only 15% did histological examination suggest the presence of inflammation (mild) when the mucosa had been judged macroscopically normal.

We conclude that although the difference between observations could be as great as 37%, these were not statistically significant overall. Histology added little to naked eye assessment. Savary grade 1 was not used in practice as no patient was reliably considered to have grade 1 oesophagitis (erythema).

Characterisation of an abnormal oesophageal clearance response in patient with oesophageal dysmotility

D WIL LiAMS, D G THOMPSON, J BANCWICZ, T O’HANRAHAN, AND M M ARPLE© (University Dept of Medicine and Surgery, Hope Hospital, Salford) Distension of the oesophagus induces clearance via an ascending excitatory and a descending inhibitory neural pathway. Patients with dysmotility have contractile abnormalities to distension which range from hypo to hyper-responsive.

We aimed to determine the nature of the hyper-responsive pattern and relation to symptoms and studied four patients with chest pain, dysphagia, and >25% non-propagating peristalsis, and 20 volunteers using a newly developed traction device to measure oesophageal clearance force. Intraluminal distension was induced with a 10 ml air filled balloon 6 cm proximal to the lower oesophageal sphincter and measured for 70 minutes.

All 20 controls responded with an increased proximal contractile activity (sum of contractions in 30 sec)=65 (40-80) mmHg (median+IQR) and distal quiescence=15 (5-20) mmHg. Associated mean clearing force was 35 (15–55) g. In contrast patients exhibited an enhanced response both proximally 120 (100-240) mmHg (p=0.055 v N) and distally 110 (95–245) mmHg (p=0.055 v N). No measurable clearance force occurred and symptoms were reproduced in all.

We conclude that the abnormal distension response of proximal and distal excitation with absent clearance force, identifies an abnormality of the descending inhibitory pathways in these patients. Relation to symptoms suggests pathophysiological relevance.

Weight reduction and gastro-oesophageal reflux

T O’HANRAHAN, M MARPLES, A BLOUNT, H SHAPIRO, C WEINKOVE, AND J BANCWICZ (University Dept of Surgery and Chemical Pathology, Hope Hospital, Salford) Weight reduction is important in treatment of gastro-oesophageal reflux. High fibre diets are unhelpful as they tend to worsen symptoms – hence compliance is poor. We assessed the value of a liquid low caloric diet (‘Cambridge’) in reflux disease. Ten patients (seven female; three male) with combined reflux disease and appreciable obesity (body mass index=35.4; range 29.8–40.6) underwent six-day weight reduction studies confirmed reflux control (‘Cambridge’). After confirming compliance, patients were receiving the Cambridge diet. Patients received dietetic supervision throughout the study. Significant weight reduction was achieved within one week and continued in seven patients who complied for the entire study (42 days) (initial weight – 87.5 kg (72.2–96.4); day seven – 84.2 (69.7–92.1) (p=0.05)*; day 24 – 80.6 (64.1–86.8) (p=0.01)*). Symptom scores improved significantly 24 hours of beginning the diet, before weight loss (initial score – 9 median (5–14); score days one to three median (0–6) (p=0.01)*). Endoscopy and pH studies confirmed reflux control at 42 days in six of seven patients who complied.

The Cambridge diet achieves weight loss and reduces reflux in obese patients. Symptomatic improvement precedes weight loss and may be related to the diet’s consistency.

*Wilcoxon’s matched-pairs signed rank test

Computer analysed ambulatory manometry of oesophageal motility

F C JEHLE, T CILUUFFO, F CASTIGLIONE, J GUYOT, C EMDE, D ARMSTRONG, J J GONIERS, AND A L BLUM (Divs of Gastroenterology, CHUV/PMU, Lausanne, Switzerland and Klinikum Steglitz, FU Berlin, West Germany) The standard method for assessing tubular oesophageal motility is stationary manometry using high amplitude, wet swallow-induced (WS) contractions. Manual analysis of WS, unlike low amplitude dry swallows (DS), is a reproducible but time consuming, observer dependent technique. We, therefore, studied 14 healthy subjects (seven male; seven female; age 22–49 years) comparing manual analysis of stationary manometry at 9 am (10 WS; 10 DS) with computer analysis of 24 hours ambulatory manometry using the first 10 spontaneous propagated contractions (SS) after 9 am the next day. Contraction amplitude differences (5 and 15 cm above lower oesophageal sphincter (LOS), between WS.
obtained in 131 'refluxers' arguably and erect or the presence of reflux criteria was associated with potential lethal complications, it requires routine hospital admission. Transendoscopic balloon dilatation (TBD) applies a controlled and radiologically directed dilating force. We report on 100 TBDs performed as an outpatient procedure in 70 consecutive patients with benign peptic stricture. Thirty eight patients were female and 32 were male: their ages ranged from 38–91 years (median 71 years). Under intravenous sedation (2–10 mg midazolam and 25–100 mg pethidine) the dilatation was performed using the 'Rigiflex TTS' balloon catheter (KeyMed) under direct vision without x-ray imaging. Upon recovery the patients were allowed free fluids and all were sent home later the same day. Forty seven patients (67%) had one dilatation only, eight patients (11%) required two dilatations, and 15 (21%) ≥ three dilatations. All patients tolerated the procedure well and had immediate symptomatic relief. One patient developed respiratory depression from over-sedation which was easily reversed. There were no other complications. A review of the outcome of the first 50 patients at the end of two years showed that five patients had died of unrelated causes and of the surviving 45, 31 could swallow all foods, 14 were having minor swallowing difficulties, and one patient was unhappy with the treatment.

Transendoscopic balloon dilatation is an effective method and can be performed safely as an outpatient procedure.

Effect of age, sex, and cigarette smoking on normal upper oesophageal sphincter function

J A WILSON, A PRYDE, A G D MARAN, AND R C HEADING (Depts of Otolaryngology and Medicine, Royal Infirmary, Edinburgh) Most recent studies of normal upper oesophageal sphincter (UOS) manometry report on less than 10 young adults. The aim of this study was to assess possible effects of age, sex, and smoking in a large number of healthy volunteers. Manometry was performed with a six sensor strain gauge assembly and a solid state recorder (Galectec GR800) in 67 volunteers (39 male, 28 female) aged 17 to 77 years, including 27 smokers. Studies were performed of lower oesophageal motility, tonic UOS pressure, and eight parameters of pharyngo-oesophageal motility during four swallows each of water and bread. Analysis was by χ², Spearman correlation, multiple regression and by unpaired Student’s t-test comparing 46 subjects aged 17–59 years with the 21 aged 60–77 years.

Increasing age was associated with reductions in distal peristaltic amplitude (p=0.001) and in tonic UOS pressure (p=0.05). Pharyngeal pressures were much greater in older subjects during both water and bread swallows (p=0.001) and UOS wave durations were reduced, with an increase in wave velocity, notably during bread swallows. These previously undescribed effects of age on pharyngeal function may compensate for reduced UOS barrier function. Women had less UOS axial asymmetry and a noticeable increase in UOS water swallow after-contraction. This may contribute to the predominance of females among globus patients, who have abnormally hypertonic UOS swallow patterns. Results were independent of smoking.

Young adults are unsuitable controls for older patients: normal values for UOS manometry are age and sex dependent.

Transendoscopic balloon dilatation of benign oesophageal strictures - a prospective study as an outpatient procedure

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W P JOYCE, A J WALKER, AND M REES (Dept of Surgery, Basingstoke District Hospital, Basingstoke) Because conventional bouginage of peptic oesophageal strictures is associated with potential lethal complications, it requires routine hospital admission. Transendoscopic balloon dilatation (TBD) applies a controlled and radiologically directed dilating force. We report on 100 TBDs performed as an outpatient procedure in 70 consecutive patients with benign peptic stricture. Thirty eight patients were female and 32 were male: their ages ranged from 38–91 years (median 71 years). Under intravenous sedation (2–10 mg midazolam and 25–100 mg pethidine) the dilatation was performed using the ‘Rigiflex TTS’ balloon catheter (KeyMed) under direct vision without x-ray imaging. Upon recovery the patients were allowed free fluids and all were sent home later the same day. Forty seven patients (67%) had one dilatation only, eight patients (11%) required two dilatations, and 15 (21%) ≥ three dilatations. All patients tolerated the procedure well and had immediate symptomatic relief. One patient developed respiratory depression from over-sedation which was easily reversed. There were no other complications. A review of the outcome of the first 50 patients at the end of two years showed that five patients had died of unrelated causes and of the surviving 45, 31 could swallow all foods, 14 were having minor swallowing difficulties, and one patient was unhappy with the treatment.

Transendoscopic balloon dilatation is an effective method and can be performed safely as an outpatient procedure.

Incidence of adenocarcinoma in Barrett’s oesophagus and an evaluation of endoscopic surveillance

R G P WATSON, K G PORTER, AND J M SLOAN (Dept of Gastroenterology, Belfast City Hospital and Dept of Pathology, Royal Victoria Hospital, Belfast) Estimates of the risk of adenocarcinoma developing in Barrett’s oesophagus vary greatly, and hence the value of endoscopic screening is controversial. We have reviewed all cases of Barrett’s oesophagus identified endoscopically between July 1976 and December 1987. There were 46 cases with circumferential involvement of at least 3 cm of the lower oesophagus. In one patient adenocarcinoma was also found at presentation and one patient was lost to follow up. In the remaining 44 the mean follow up period was 3.5 years. One patient was subsequently...
diagnosed as having adenocarcinoma – an incidence of one per 154 patient years follow up.

During 1988, 29 cases were examined endoscopically at least one year after first diagnosis (mean 3.7 years). Biopsy specimens were taken systematically at 1 cm intervals in each case and from the margins of ulcers in seven patients. No adenocarcinomas were found (incidence zero per 108 patient years) but six had dysplasia (five mild, one moderate) in macroscopically normal mucosa.

It is concluded that the incidence of adenocarcinoma is relatively small. The detection of dysplasia is inadequate if only macroscopically abnormal areas are biopsied and it is recommended that biopsies are taken systematically.

Surgery for para-oesophageal hiatus hernia: the treatment for all ages

M I HALLISSY, J G TEMPLE, AND D A RATLIFF (Queen Elizabeth Hospital, Birmingham)
The surgical treatment of a sliding hiatus hernia remains an incidental feature of surgery for reflux. With para-oesophageal hernia, surgery is recommended to prevent the life threatening complications of incarceration. The advanced age of many patients with this condition, however, makes many surgeons reluctant to offer elective surgery. The results of treatment in 19 patients under the care of one consultant are described. The age of the patients ranged from 37 to 81 years with a mean of 68.2 years. The group of 15 females and four males all underwent surgery, three as urgent cases due to incarceration and the remainder as elective ones. There was one death in each group, giving an overall hospital mortality of 10.5%. Over a follow up period of up to five years, 13 (76.5%) have remained symptom free. Two have reflux controlled by medical treatment and one patient has developed a carcinoma.

These results confirm the safety of elective surgical treatment and its effectiveness in controlling symptoms. Delaying treatment until complications develop increases mortality six-fold. All cases of para-oesophageal hiatus hernia should be referred for a surgical opinion.

Recurrence of abnormal acid reflux after antireflux surgery: study by serial ambulatory intraoesophageal pH monitoring

S J WALKER, S HOLT, C J SANDERSON, AND C J STODDARD (University Dept of Surgery, Royal Liverpool Hospital, Liverpool) Little is known about the recurrence of acid reflux after antireflux surgery (ARS), and whether this can be predicted by early postoperative ambulatory pH monitoring (pHm).

We prospectively studied 24 patients (20 males, four females), mean age 48 years (range 23-66) with refractory gastro-oesophageal reflux. Standardised pH monitoring (pHm) was performed before and at one week and three months after transabdominal ARS (18 Nissen total fundoplication, six Lind partial fundoplication). In 10 patients repeat pHm was undertaken at one year. Six parameters of reflux were examined at five pH levels by 22 hour pHm (Ormed Ltd). ARS significantly improved the median results (IQR) of all pHm parameters compared with no treatment (p<0.05, Wilcoxon’s signed-rank test at pH 4).

Overall there was no significant difference between the results obtained at one week, three months, and one year. The pHm one week after ARS correctly predicted a normal or abnormal result at three months of 18 of 24 (75%) patients. At one week after ARS the results of pHm were abnormal in 3-24 (12.5%) patients increasing at three months to 9-24 (37.5%). At one year a further two of 10 patients had developed abnormal pHm results.

We conclude that: (1) The results of pHm are significantly improved by ARS and are in general maintained over the first year. (2) A minority of patients may develop abnormal pHm results immediately or at any time during the first year after ARS.

Oesophageal asthma: episodic dysphagia with eosinophilic infiltrates

S E A ATKINWOOD, T C SMYRK, AND T R DEMEESTER (Creighton University, Omaha, Nebraska, USA) Small numbers of interepithelial oesophageal eosinophils (IEE) may be seen occasionally in normal volunteers and in 50% of patients with gastrooesophageal reflux disease. High concentrations of IEE are rarely seen.

During the past two years we have identified 15 patients with high concentrations of eosinophils in oesophageal biopsy specimens (defines as >10 IEE/high power field). Dysphagia was the presenting complaint in each patient. No evidence of anatomical obstruction or endoscopic oesophagitis was seen on endoscopy and all had normal oesophageal acid exposure on 24 hour pH monitoring. In contrast, among 100 patients with increased oesophageal acid exposure only three had high concentrations of IEE. Oesophageal manometry on the 15 patients with high concentration of eosinophils showed a motility disturbance in 80% of these patients but without a characteristic pattern.

The high prevalence of abnormal motility in these patients suggest that IEE maybe a histological marker of a motility disorder. The finding of high concentrations of IEE in the oesophageal biopsy specimens from patients with dysphagia, no obvious stricture, and normal 24 hour oesophageal pH monitoring represents a distinct clinical syndrome. This abnormality may be succinctly described as ‘oesophageal asthma’.

Omeprazole provides faster healing and symptom relief of reflux oesophagitis than cimetidine

C M BAILE, P W N KELING, C A O’MORAIN, S P WILKINSON, R A MOUNTFORD, J M TEMPERLEY, D N FOSTER, R F HARVEY, D G THOMPSON, I C FORGAC, K S BASSETT, P D J RICHARDSON, AND THE ROCOCO INVESTIGATOR GROUP (Gastroenterology Units in Wigan, Dublin, Gloucester, Bristol, Preston, Rochdale, Salford, Dulwich, and Astra Pharmaceuticals Ltd, England) This double blind, multicentre study compared healing, symptom relief, and tolerability of omeprazole (OM) with cimetidine (CI) in the treatment of reflux oesophagitis. Two hundred and seventy two patients with endoscopically verified symptomatic reflux oesophagitis were randomised to receive OM 20 mg (n=138) or CI 400 mg qds (n=134) for four or, if necessary, eight weeks.

At four weeks, endoscopic healing had occurred in 56% OM vs 26% CI (p<0.001), and at eight weeks in 71% OM vs 35% CI (p<0.001) patients. At four weeks, 46% OM vs 22% CI patients were symptom free (p<0.001); the corresponding figures for patients were 66% OM vs 41% CI (p<0.001). At entry, 66 of 104 (63%) OM patients and 56 of 94 (60%) CI patients, for whom data were available, had abnormal oesophageal histology; on completion of the study, 75% OM vs 65% CI (p<0.05) had histological healing. Diary card data (days two to 14) showed OM patients had faster relief of day and nighttime reflux symptoms and consumed fewer antacids than CI patients (p<0.001). Both drugs were well tolerated.
This study shows that omeprazole 20 mg once daily provides faster healing and symptom relief of reflux oesophagitis than cimetidine 400 mg four times daily.

**Full dose H₂ receptor antagonist prophylaxis does not prevent relapse of reflux oesophagitis**

**D ARMSTRONG, A L BLUM, AND THE REZITIC STUDY GROUP (Div of Gastroenterology, CHUV/PMU, Lausanne, Switzerland)** As low dose ranitidine does not prevent reflux oesophagitis relapse, we conducted a randomised, double blind, placebo controlled study of six months full dose ranitidine prophylaxis. After endoscopically proved healing, 193 patients with oesophagitis (Savary grade I) took ranitidine, 150 mg bd (R150) or 300 mg noct (R300) (to study the effect of nocturnal acid suppression) or placebo. Exclusion criteria were: unhealed oesophageal strictures, intercurrent illness, gastric stasis, previous upper gastrointestinal tract surgery, or poor compliance. Relapse was assessed symptomatically every two months and endoscopically at six months. The groups were age and sex matched: R150 (50 male, 14 female; age mean (SD) 49-1 (15-4) years), R300 (48 male, 14 female; 49-6 (14-0)), P (41 male, 14 female; 46-6 (13-4)): 13 patients failed to follow up.

Crude endoscopic relapse rates (life table estimates) were R150: 23 of 64 (37-5%), R300: 25 of 61 (41-0%), P: 24 of 55 (45-1%). Endoscopic or symptomatic relapse rates in the three groups were never significantly different (log rank test). At six months, symptomatic relapse was less than endoscopic relapse in all groups.

We conclude that full dose ranitidine, taken at night or twice daily, does not prevent recurrent reflux oesophagitis or symptoms.

**Plasma pancreatic polypeptide response to insulin hypoglycaemia after antireflux surgery**

**E H JANSEN, J M I M HORBACH, J B M J JANSEN, W P M HOPMAN, H G GOOSZEN, AND C B H W LAMERS (Depts Gastroenterology and Surgery, University Hospital Leiden and Nijmegen, The Netherlands)** Based on the observation that patients occasionally develop symptoms suggesting vagal damage after surgery for gastro-oesophageal reflux disease (GORD), we have studied the pancreatic polypeptide (PP) secretion in response to hypoglycaemia, as indicator of vagus nerve function, in 20 patients with Belsey-Mark IV antireflux surgery (12 female, eight male; mean age 52 years), in 24 patients with Nissen fundoplication (10 female, 14 male; mean age 52 years), in nine non-operated patients with severe GORD (four female, five male; mean age 48 years), in six patients with truncal vagotomy (five female, one male; mean age 47 years), and in 20 normal control subjects (six female, 14 male; mean age 48 years). All subjects had a plasma glucose trough of less than 2-5 mmol/l after intravenous injection of 0-1 U/kg insulin. In the normal subjects plasma PP increments ranged from 94 to 730 pM. Eight of 20 (40%) of the patients with the Belsey-Mark IV procedure (p<0-01), seven of 24 (29%) of patients with Nissen fundoplication (p<0-05), all six patients after truncal vagotomy (p<0-01), but none of the non-operated patients with GORD had plasma PP responses to the insulin hypoglycaemia below the lowest value in the control subjects.

It is concluded that patients with antireflux surgery often have an abnormal plasma PP response to insulin hypoglycaemia. Although this abnormality is probably caused by vagal damage during surgery, prospective studies are needed to elucidate the exact mechanism and to establish the clinical importance of this finding.

**Omeprazole or high dose ranitidine in the treatment of patients with reflux oesophagitis not responding to standard doses of H₂ receptor antagonists**

**I LUNDELL, I H WESTIN, S SANDMARK, L-C ENDiNDER, L BACKMAN, P UNGE, B SANDZÉN, AND O FAUSA (Sahlgrenska sjukhuset, Göteborg, AB Hässle, Mölndal, Region sjukhuset Orebro, Centralsjukhuset, Karlstad, Danderyds sjukhus, Danderyd, Stockholm, Peter Uinge, Sandvikens sjukhus, Sandviken, Regionsjukhuset, Umeå, Rikshospitalet, Oslo)** Ninety eight patients with erosive or ulcerative oesophagitis unhealed after at least three months' treatment with cimetidine (±1200 mg daily) or ranitidine (±300 mg daily), were randomised to treatment with either omeprazole 40 mg once daily, or high dose ranitidine 300 mg bd. Treatment was given for four to 12 weeks. Endoscopy, symptom assessment, and laboratory screenings were performed every fourth week. Endoscopic healing was defined as complete epithelialisation of all macroscopic erosions or ulcers.

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Sixty three per cent of the omeprazole treated patients were healed after four weeks' treatment compared with 17% of the patients treated with ranitidine. The corresponding figures after eight weeks were 86% and 38%, and at 12 weeks, 90% and 47%, respectively. The difference was highly significant for all treatment periods, p<0-0001. After four weeks' treatment heartburn had resolved completely in 86% of patients treated with omeprazole compared to 32% in the ranitidine group (p<0-0001).

In patients with oesophagitis that does not respond to standard doses of H₂ receptor antagonists, omeprazole 40 mg daily is superior to high dose ranitidine in healing erosions or ulcers and in relieving symptoms.

**Combined intracavitary and external beam radiotherapy in the treatment of oesophageal carcinoma**

**M B CLAGUE AND P J D K DAWES (Depts of Surgery and Radiotherapy, Newcastle General Hospital)** Forty two patients referred to the regional radiotherapy department with oesophageal neoplasia (32 squamous and 10 adenocarcinoma; tumour length 1-10 cm) were treated by combined external beam therapy (30-50 Gy in 10-20 fractions over two to five weeks) followed by intracavitary therapy (10 Gy at 1 cm), using an endoscopically inserted after-loading technique (Selectron).

There were no deaths related to the endoscopic procedure. Swallowing was restored in most patients, although seven (17%) have developed benign strictures requiring dilatation and four (10%) recurrent tumour requiring intubation. One (2%) patient developed an oesophagotraheal fistula. Probability of survival was calculated at 82% at three months, 60% at six months, and 50% at nine months. This combined mode of therapy is well tolerated and associated with few complications. Long term results of patients with an otherwise poor prognosis are awaited.

**Is endoscopic intubation of adenocarcinoma affecting the cardia worthwhile?**

**S Y HIKHAR, C S ROBERTSON, AND M ATKINSON (Dept of Surgery, University Hospital, Nottingham)** Palliation of dysphagia by...
endoscopic placement of a prosthetic oesophageal tube has generally been considered to be less satisfactory in adenocarcinoma affecting the cardia than in squamous oesophageal cancer. In this study the outcome after intubation in 144 patients with adenocarcinoma has been compared with that in 125 with squamous carcinoma. Both groups were comparable in age, duration of dysphagia, weight loss, length of the growth, and size of the tube inserted. There was a significant preponderance of men (75%) in the adenocarcinoma group compared with the squamous group (50%). A higher incidence of instrumental perforation was found in the adenocarcinoma group (16-7% compared with 9-6%) but this only reached statistical significance when growths affecting the cardia were compared with those confined to the oesophagus irrespective of histological type. Relief of dysphagia, proce-
dural mortality, and longterm survival were not related to either the histological type or the anatomical involvement by the growth.

It is concluded that although carcinoma involving the cardia carries a higher perforation rate at endoscopic intubation, there is no difference in symptomatic relief or immediate or longterm survival compared with growths limited to the oeso-
phagus, irrespective of histological type. Endoscopic intubation is a worthwhile pro-
cedure in adenocarcinoma of the cardia.

Strength of oesophageal contractions can be controlled voluntarily

R M Valori, M T Halliday, and J A Dunn
(Queen Elizabeth Hospital, Birmingham)

There is substantial variation in the amplitude of oesophageal contractions within individuals. This study explored the hypothesis that by varying the size of a swallow, oesophageal peristalsis can be altered. Oesophageal pressures were measured 3, 8, and 13 cm above the lower sphincter in six healthy volunteers and eight patients with atypical chest pain. The volunteers performed 40, 5 ml wet swallows and 40 dry swallows, and the patients 20, 5 ml wet swallows. With each swallow the subjects were instructed, in random order, to take either a little swallow or a big gulp. Mean amplitudes were compared using analysis of variance.

None of the subjects experienced difficulty in varying the size of his swallows. In both groups the mean amplitude of contractions was significantly greater for big gulps than little swallows (p<0.0001). This was true for wet (82.1 v 70.0 mmHg) and dry swallows (52.3 v 43.3 mmHg). For the patients’s wet swallows the values were 68.8 and 52.9 mmHg.

Thus, the amplitude of oesophageal peristaltic contractions can be controlled voluntarily by the size of swallow. This effect may account for some of the within subject variation in the amplitude of oesophageal contractions. During oesophageal manometry subjects should be encouraged to standardise their swallows whenever possible. Patients with dysphagia or gastro-

In the human fetus and infant.

Effect of protein and lactulose on the production of gamma amino butyric acid by faecal escherichia coli

H A Mardini, D A Burke, B Al Jumahli, and C O Record
(The Liver Unit, Royal Victoria Infirmary and University of Newcastle Upon Tyne)
The mechanism whereby lactulose ameliorates hepatic encephalopathy (HE) remains unknown, but an alteration in the bacterial production of gamma amino butyric acid (GABA) in the gut is a possible mode of action. The aim of this study was to investigate the effect of protein and lactulose on the production of GABA by faecal E coli. Using the rat synthetic mem-
brane assay and gas chromatography/mass spectrometry the production of GABA by faecal E coli with and without the addition of albumin, haemoglobin, blood, and lactulose under aerobic and anaerobic conditions was determined. Routine culture media gave high background counts of GABA making them unsuitable. Using an inorganic media that gave minimal background counts, maximal GABA production was found to occur between 12 and 30 hours. Mean GABA produced aerobically after 30 hours at 37°C by a single strain was 101 (14.8) μmol/l (99% cl 87–114 μmol/l). GABA production was significantly increased by the addition of albumin (333 (15.8) μmol/l p<0.001) and haemoglobin (286 (8.2) μmol/l p<0.001). GABA production under anaerobic conditions was 20% of that produced aerobically but albumin and haemoglobin increased production by >700%. Lactulose did not seem to attenuate significantly GABA production under aerobic or anaerobic conditions.

These data confirm that GABA is produced by faecal E coli, that protein noticeably enhances its production and suggests that lactulose does not exert its effect by attenuating GABA production.

Age related changes in copper associated protein and metallothionein in the liver of the human fetus and infant

LIVER POSTERS

Thrombocytopenia in liver disease: an immune phenomenon?

R DE Noronha, B Taylor, M Greaves, and D R Triger
(University Depts of Haematology and Medicine, Royal Hallamshire Hospital, Sheffield)
Thrombocytopenia commonly complicates liver disease. The pathogenesis is multifold: hypersplenism, immuno-
suppressive therapy, consumptive coagulopathy, and alcohol ingestion are all potenti-
ally contributory. In some subjects the degree of thrombocytopenia is excessive. We have therefore measured platelet count, serum IgG, platelet associated IgG (PAIgG) by radial immunodiffusion, serum IgG immune complexes (IC) by polyethyl-
leneglycol precipitation, and assessed severity of liver disease using Child’s score, in auto-immune chronic active hepatitis (CAH n=27), alcoholic liver disease (ALD n=27), and primary biliary cirrhosis (PBC n=38), as well as in normal healthy subjects (n=13). The PAIgG was increased in 52% of subjects with liver disease (48% with CAH, 47% with PBC, and 64% with ALD) and correlated with serum IgG (r=0.25 p=0.034) and with platelet count (r=.0.25 p=0.013) in the whole population. An inverse correlation was noted between Child’s score and both platelet count (r=−0.49 p<0.001) and PAIgG (r=0.22 p= 0.034). In subjects with CAH and thrombo-
cytopenia (platelet count <150×10⁷/l) (n= 11) PAIgG and IC correlated inversely with platelet count (r=−0.69 p=0.04) (r=−0.67 p=0.025) and PAIgG with IC (r=−0.88 p= 0.002).

These results indicate increased platelet immunoglobulin binding in all forms of chronic liver disease, particularly with increasing severity of liver failure and degree of thrombocytopenia, and suggest a role for immune-mediated mechanisms in CAH possibly through immune complex formation. These findings are of potential therapeutic importance in subjects with primary haemostatic failure in liver disease.
confirmed necrotic changes as did biopsy of the liver lesions treated. In two patients, tumour size has remained static (follow up 11 and three months), and in one growth rate was reduced. ILH with US guidance offers a precise, safe way to cause thermal necrosis in liver secondaries with reduction in growth rate and could have a place in their treatment.

Cell mediated immunity does not change after relief of obstructive jaundice in man

R F PACE, R GONZAGA, E KAMINSKY, H HODGSON, AND I S BENJAMIN (Hepatobiliary Surgery Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London) Impaired cell mediated immunity (CMI) has been described in obstructive jaundice and attributed to depressed serum factors or to depressed intrinsic T cell function. We studied lymphocyte responsiveness to PHA, the in vitro correlate of T cell function, in nine patients before and after relief of biliary obstruction (four cholangiocarcinoma, four pancreatic carcinoma, one colorectal hilar metastases). Treatment consisted of surgical bypass in four, and internal biliary stenting in five patients. Peripheral blood mononuclear cells were stored at −70°C until studied. Cultures were performed in 10% autologous serum obtained before (mean serum bilirubin 302 μmol/l) and after treatment (24 μmol/l), as well as in 10% fetal calf serum.

No depressant effect on icteric serum was shown, either on patients’ cells, or on normal donor cells. Similarly, there was no evidence of diminished intrinsic T cell responsiveness reversed by biliary drainage. The results do not support a significant reduction in CMI attributable to the presence of obstructive jaundice.

Cystic fibrosis related liver disease – do common bile duct strictures have an aetiologic role?

S Ó’BRIEN, M KEOGAN, M CASPY, M X FLIZ-GERALD, AND J E HEGARTY (Gastroenterology and Liver Unit, Adult Cystic Fibrosis and Depts of Radiology and Nuclear Medicine, St Vincent’s Hospital, Dublin) Recent studies have implicated common bile duct strictures as an aetiological factor in cystic fibrosis (CF) related liver disease.

We have evaluated the intra- and extrahepatic biliary tree in 26 patients with CF (mean age 19 years). Sixteen patients had clinical (hepatomegaly/splenomegaly), biochemical (abnormal liver function tests of six months duration) or histologic (cirrhosis/fibrosis/fatty change) evidence of liver disease.

The biliary tree was evaluated using real time ultrasound (US) (26 patients). “Tc diisopropyl iminodiacetic acid (DISIDA) biliary scintigraphy (22 patients. 12 with liver disease), and endoscopic retrograde cholangiography (ERC) (13 patients with liver disease).

Ultrasound examination in 26 patients showed no evidence of intra- or extrahepatic bile duct dilatation: ERC showed normal intra- and extrahaepatic bile ducts in 13 patients. The % excretion of DISIDA at 45 (E45) and 60 (E60) minutes was diminished in the 12 patients with liver disease when compared with 10 patients without liver disease. (E45=39.8% ± 65.8% and E60=49.7% ± 76.3%, respectively; \(p<0.01\)). Kruskal Wallis analysis of variance.) The mean extrahepatic biliary tract transit time of DISIDA was prolonged in the patients with liver disease, 23.3 minutes compared with nine minutes in the patients without liver disease \((p<0.05\) Wilcoxon’s rank-sum test).

In view of the normal biliary anatomy shown by ERC, the delayed biliary excretion of DISIDA may be explained by biliary hypomotility and functional stasis. We conclude that CBD strictures are not a factor in determining the development of liver disease in this population of patients with CF.

Hepatitis B virus (HBV) DNA characteristic of viral replication in endotoxin stimulated mononuclear cells of HBV carriers

J DAVISON, H DANIELS, G ALEXANDER, AND R WILLIAMS (Liver Unit, King’s College Hospital, London) Previous studies have consistently shown that mononuclear cells from hepatitis B virus (HBV) carriers contain 3-2 Kb HBV DNA. The importance of this observation is still not clear, and firm evidence that mononuclear cells support production of HBV has been lacking. DNA was extracted from the peripheral blood mononuclear cells of 12 established HBV carriers after 0, 48, and 96 hormone culture with or without endotoxin to activate cells and stimulate cell division. Southern blots of this DNA were probed with cloned HBV DNA. Low molecular weight HBV DNA (1-6–2-8 Kb) characteristic of active viral replication was identified in both unstimulated and stimulated cell preparations of three patients, although the proportion of
HBV DNA was greater in endotoxin stimulated preparations. In a further two subjects, a different spread of low molecular weight HBV DNA (approximately 0.4–1.5 Kb) was identified in endotoxin stimulated preparations. In both of these, mononuclear cells harvested at zero time were negative for HBV DNA.

The presence of HBV DNA in stimulated, cultured mononuclear cells, with a pattern suggestive of viral replication seen in this study, is of potential importance since HBV genes have been shown to modulate interferon production.

Liver metastases: treatment by cryotherapy

R M CHARNLEY, J DORAN, and D J MORRIS (Dept of Surgery, University Hospital, Nottingham) We have developed a new design of cryoprobe which enables freezing of an intrahepatic lesion with minimal destruction of surrounding tissue. The cryoprobe has a 5 mm diameter shaft and a copper tip through which liquid nitrogen circulates at –196°C. The probe is inserted into the lesion at laparotomy under intraoperative ultrasound control and coolant is circulated producing a sphere of liver destruction, the size of which can be monitored by intra-operative ultrasound.

Ten patients with liver tumours (nine with metastases; seven colorectal, one carcinoid, and one ovarian; one older patient with a primary liver cancer) have undergone cryotherapy of a total of 44 intrahepatic lesions (range: one to 12 lesions per patient), eight of which were impalpable and detectable only by intraoperative ultrasound. All patients were discharged home five to 10 days post-operatively. Four colorectal cancer patients have been followed up for three months or more and in three of these serum CEA values have decreased – in one patient to undetectable levels. Computed tomograms have shown defects in the liver substance corresponding to the frozen metastases.

Cryosurgery of the liver using this novel system may provide an alternative technique for the treatment of primary and secondary liver tumours.

Hepatitis B virus DNA in fibrolamellar variant of hepatocellular carcinoma

F DAVISON, E A FAGAN, O DIETZE, B PORTMANN, and R WILLIAMS (Liver Unit, King’s College Hospital and School of Medicine and Dentistry, London) Two patients with the fibrolamellar variant of hepatocellular carcinoma were found to be seropositive for HBsAg and anti-HBc. DNA from tumour and non-tumorous areas of each liver was examined by molecular hybridization for hepatitis B virus (HBV) DNA sequences. Undigested DNA from each tumour gave high molecular weight smears. Restriction enzyme digestion, in patient 1, produced high molecular weight bands suggesting two points of HBV DNA integration into hepatocyte chromosomes. In patient 2, the analysis indicated a single instance of integration. In the non-tumorous liver tissue in both cases, undigested DNA showed episomal (3.2 Kb) HBV DNA as well as high molecular weight bands. As with the typical HBV related hepatocellular carcinoma, restriction enzyme digestion of non-tumours liver, in patient 2, yielded a different pattern of high molecular weight bands indicating that the virus genome had integrated at different chromosomal locations from that seen in the tumour.

The finding of integrated HBV DNA, especially in tumorous as well as non-tumorous liver, would be consistent with an oncogenic role for HBV in certain instances of fibrolamellar tumours, as well as in the more typical HBV related hepatocellular carcinoma.

Relation of neutrophil elastase and its inhibitor to infection in fulminant hepatic failure

P G LANGLEY, R D HUGHES, N ROLANDO, and R WILLIAMS (Liver Unit, King’s College Hospital and School of Medicine and Dentistry, London) Elastase, a proteolytic enzyme released during neutrophil activation, has been implicated as a cause of cell damage in multi-organ failure due to sepsis, which frequently occurs in patients with fulminant hepatic failure (FHF). Increased blood concentrations of the complex formed with its inhibitor alpha1-antitrypsin (alpha1-AT) indicate release of elastase into the circulation. In the present study we have measured elastase and alpha1-AT complex by ELISA in 31 patients with FHF (26 paracetamol overdose, five virus). Values on admission were significantly increased compared with normal [mean (SE) 689 (85) Âµg/l v 37 (16) Âµg/l, n = 10, p<0.001]. In patients with bacteriologically proved infection, values were significantly increased [887 (146) Âµg/l, n = 11] compared with no infection [429 (114) Âµg/l, n = 11; p<0.05]. Values were significantly lower in patients who survived [561 (113) Âµg/l, n = 18] than in those who did not [866 (114) Âµg/l, n = 13; p<0.05]. alpha1-AT was present at normal concentrations in FHF (100 (6)% compared with 97 (6)% in controls), but was significantly greater in patients who survived (117 (7)% compared with those who did not (76 (6)%, p<0.05). Immunological alpha1-AT in FHF (103 (7)% correlated with enzyme activity (r=0.87, p<0.001).

These results confirm that neutrophils are activated in FHF and this is associated with septicaemia. The capacity to inhibit elastase activity may be important for limiting the consequences of sepsis in FHF.

Endoscopic sclerotherapy and management of gastric variceal haemorrhage

A E S GIMSON, D WESTARY, and R WILLIAMS (Liver Unit, King’s College Hospital and School of Medicine and Dentistry, London) Although injection sclerotherapy is of proved benefit in oesophageal variceal haemorrhage, its value in the management of gastric variceal bleeding is less clear. A retrospective study was therefore performed of 47 episodes of acute gastric variceal haemorrhage in 41 patients who were treated by endoscopic sclerotherapy. Gastric variceal haemorrhage was classified according to the site: from the lesser curve (group 1) in 13, within a hiatus hernia (group 2) in six, and fundal or without oesophageal varices (type 3) in 22 subjects. Previous oesophageal varix haemorrhage had occurred in 28 (69%) patients and varices were obliterated by sclerotherapy in eight before first gastric variceal bleed. Haemostasis was achieved by sclerotherapy in 54%, 71-4%, and 26% respectively, tissue adhesive (Bucrylate) being used in two patients in group 3. After additional measures (balloon tamponade or surgery) group 1 (85%) had stopped bleeding significantly more frequently than group 3 (44-4%). More patients in group 3 died due to uncontrolled bleeding (41%) than in group 1 (7-7%). Hospital mortality depended on the severity of the liver disease with 15% of Child’s grade A and 56% of grade C cases dying.

We conclude that endoscopic sclerotherapy of gastric varices should be reserved only for lesser curve of hiatal varices and that early surgery (or endoscopic tissue adhesive) be considered for fundal variceal haemorrhage.

Hepatic perfusion index – pause for thought

D HEMINGWAY, S GRIME, D M NOIT, D CHANG, S A JENKINS, and I COOKE (University Dept of
Surgery, Royal Liverpool Hospital, Liverpool) The hepatic perfusion index (HPI) derived by dynamic hepatic scintigraphy (DHS) predicts the presence of micro-metastases in man. We have shown similar alterations in the HPI of rats with hypervascular hepatic tumours and established that these changes resulted from a decrease in portal venous inflow (PVI) and arteriovenous shunting. We have now repeated these studies on hypovascular tumours which are more representative of those found in man.

Hepatic and systemic haemodynamics, arteriovenous shunting and HPI were determined in rats two, six, 10, and 20 days after intraperitoneal administration of 10^6 HSN sarcoma cells. Overt hepatic tumour was present at 20 days. However, the HPI in animals with tumour (47.2 ± 4.1) was only significantly greater (p<0.002, Student's t-test) than in controls (35.2 ± 2.9) at 10 days and remained raised at 20 days. Hepatic artery flow was unchanged throughout the study but PVI was significantly decreased (p<0.002) at 10 and 20 days. No arteriovenous shunting occurred during the growth of the tumour.

These results indicate that in slow growing hypovascular hepatic tumours, changes in the HPI occur late in their development and are related to a reduction in PVI, suggesting that DHS may not predict very early tumours in man.

Effects of somatostatin on portal venous washout of a labelled marker administered via the hepatic artery

D M Nott, J Yates, T Cooke, and S A Jenkins (University Dept of Surgery, Royal Liverpool Hospital, Liverpool) The prognosis of patients with liver metastases derived from colorectal carcinoma is poor, and is not significantly improved by regional chemotheraphy. We have previously shown that portal venous flow is responsible for the washout of a large proportion of a regionally injected marker substance (representing cytotoxic drug) from the liver. The aim of this study was to establish whether the vasoactive drug somatostatin could reduce portal venous washout of a radiolabelled marker.

Portal venous washout was studied in Fischer rats using a scintillation counter placed over the thorax. 20 MBq of "Technetium Methylene Diphosphonate (MDP) in a volume of 0.025 ml was injected via the hepatic artery and its washout from the liver measured before and during intra-venous infusions of saline or somatostatin (2 µg/hour). With both infusions to the liver clamped 18 (5)%) of the MDP passed through the liver into the systemic circulation, significantly less than when only the hepatic artery flow was occluded (86 (4)%). Thus during saline infusion the portal vein washout of marker was 64 (6)%. During somatostatin infusion, portal venous washout of the market was significantly reduced, 53 (2)% (p<0.05, Mann Whitney) compared with saline infusion.

The results of this study suggest that concomitant administration of somatostatin during regional chemotherapy of the liver reduced the portal venous washout and may therefore potentiate uptake of the cytotoxic by the tumour.

Postprandial changes in portal haemodynamics in patients with cirrhosis

S O'Brien, M Keoghah, N Afshah, S Patchet, and J E Hegarty (Gastroenterology and Liver Unit, St Vincent's Hospital, Dublin) Previous studies have shown that portal venous pressure (PVP) increases in patients with cirrhosis after a protein meal. Because this increase in PVP may be due to an increase in hepatic blood flow (HBF) or hepatic vascular resistance (HVR), the present study was designed to examine the precise relation between postprandial changes in PVP, HBF, and HVR in patients with cirrhosis.

Estimated hepatic blood flow (EHBF; indocyanine green clearance), porto-systemic gradient (PSG; wedged-free hepatic venous pressure), and post-systemic vascular resistance (PSF; PSG/EHBF) were simultaneously determined before and at 10 minute intervals after a high protein meal, containing 80 g protein, 40 g carbohydrate, 12 g fat, (600 kcal) in nine patients (seven alcoholic, two non-alcoholic) with cirrhosis and portal hypertension.

After the meal, mean PSG increased by 33% from mean (SEM) 15-6 (0-97) mmHg to 20-66 (1-3 mmHg (p<0.01; Wilcoxon's signed rank test) within 30 minutes. Coincident with this rise in PSG, EHB increased by 76% from 20-6 (1-9) ml/min/kg to 26-3 (3-5) ml/min/kg (p<0.01) within 30 minutes, at which time PSR had decreased by 33% from 1-08 (0-08) 10^-5 ml/min/mmHg to 0-72 (0-05) 10^-5 mmHg/ml/min (p<0.01).

These results suggest that the post-prandial increase in PVP in patients with cirrhosis is mediated by an increase in HBF and modified by a simultaneous decrease in PSR.

Effects of constant infusion of somatostatin, sandostatin, and vasopressin on portal pressure and collateral blood flow in portal hypertensive rats

J Yates, D Nott, S Ellenbrown, D Billing, I Cooke, S A Jenkins, and R Shields (University Dept of Surgery, Royal Liverpool Hospital and Dept of Medical Biochemistry, Liverpool Polytechnic, Liverpool) Bolus injections of somatostatin and its analogue sandostatin noticeably reduce collateral blood flow in portal hypertensive rats but vasopressin has little effect. This study is designed to investigate whether the effects on portal pressure (PP) and collateral blood flow are maintained when these vasoactive drugs are given by constant infusion.

Rats made portal hypertensive by partial portal vein ligation, were infused over 30 minutes with vasopressin (0.08 µU/g/h), somatostatin (0.4 µg/h), sandostatin (0.4 µg/h), or saline. Systemic haemodynamics and PP were monitored continuously and collateral blood flow was measured by consecutive intrasplenic injections of "Tec-methylene-diphosphonate and "Tc-albumin microspheres before and one, ten, 20, and 30 minutes after the start of the infusions.

All vasoactive drugs significantly reduced PP, vasopressin being the most effective. Collateral blood flow was significantly decreased (p<0.001, Student's paired t-test) after infusion of somatostatin (60-6 (7-8) to 36-1 (7-5)%) and sandostatin (50-0 (7-9) to 12-9 (3-0)%). In contrast vasopressin infusion significantly increased collateral blood flow (46-5 (16-8) to 62-5 (18-2); p<0.01).

As the efficacy of vasoactive drugs in controlling variceal haemorrhage depend on their ability to reduce collateral blood flow, somatostatin and its analogue are the most effective in this respect.

Macrophages and fibroblast may enhance metastatic growth in the liver

M Loizidou, R Lawrence, N Carty, A Cooper, P Alexander, and T Taylor (University Surgical Unit, Southampton General Hospital, Southampton) After partial hepatectomy followed by intraportal tumour injection, a process associated with regeneration was shown to promote metastatic growth within rat livers. Maximal tumour take occurred when the partial hepatectomy was performed four to seven days before injection.

We studied the influence of monocytes...
and littoral cells on tumour growth. Samples were taken from regenerated rat livers (zero to 10 days after hepatectomy (PH)) and examined by immunocytochemistry, in vitro culturing and autoradiography.

For days zero to two PH only, Kupffer cells failed to stain with a monoclonal antilysozyme antibody and were also relatively unavailable for enzymatic disaggregation for culture. They were still present, however, as zero to two day PH livers were able to phagocytose intraperitoneally administered carbon.

Cultures of dissociated livers contained macrophages and littoral cells. Within three days of culture rapid growth of fibroblasts occurred in the four to six day PH preparations. Other preparations yielded fibroblasts after eight days, but the difference was still obvious at low power cytology after 10 days. Additionally, fibroblasts seemed to proliferate at day four PH, judged by autoradiography.

In conclusion, fibroblast activity and restoration of macrophage function are synchronous with maximum tumour take.

**Prognostic models in primary biliary cirrhosis**

H C MICHISON, P J KELLY, AND O F W JAMES (University of Newcastle upon Tyne, Dept of Medicine (Geriatrics), Newcastle upon Tyne) The importance of prognostic information in primary biliary cirrhosis (PBC) has increased with reliable transplantation for late disease and more possible treatments for early disease. The data base for prognostic assessment is critical. We used Cox’s proportional hazards model to examine the following variables in 193 cases of PBC at diagnosis: age, log⁷ bilirubin, albumin, presence or absence of cirrhosis, and symptoms. Mean age was 58 years, range (23-79), median follow up 65 months (36-233).

In the whole group symptom status was not apparently linked (because linked to bilirubin and cirrhosis, both more significant) but all others were (age: coefficient 0·0398, p=0·009, log⁷ bilirubin: 0·8784, p<0·0001, albumin: 0·0553, p=0·042, cirrhosis: 1·7781, p<0·0001). If only the 114 symptomatic patients were analysed, albumin was no longer of prognostic value. If only the 79 asymptomatic patients were analysed, only albumin and cirrhosis significant. Thus the change in coefficients of significant variables result in the three models predicting different survival rates.

Asymptomatic patients had normal survival (! controls) until symptoms developed. Thus, the above models are not useful for patients remaining asymptomatic. Accurate prognostic information for symptomatic patients should be based on data drawn from symptomatic patients alone as the addition of data from asymptomatics is confounding.

**Increased soluble serum T8 levels in primary biliary cirrhosis**

K I NOURI-ARIA, M LOMBARD, A I W F EDDLESTON, AND R WILLIAMS (Liver Unit, King’s College Hospital and School of Medicine and Dentistry, London) Reduced suppressor cell number and function have been described in a number of autoimmune diseases and may contribute to pathogenesis. Suppressor cell function depends upon the interaction of T8 antigen with other limbs of immune system. In the present study soluble serum T8 (the antigen present on suppressor/cytotoxic population) values were measured in the sera of 23 patients with primary biliary cirrhosis (PBC), five with hepatitis B virus (HBV) infection, and 21 normal subjects (NS) using an enzyme immunoassay. The proportion of cells expressing the T8 antigen and the intensity of its display were also determined using an immunofluorescent technique and an ELISA respectively for 12 PBC and 10 NS.

The soluble serum T8 levels were significantly higher in PBC (mean (SD) units/ml 776 (323)) than NS (322 (112)) or the HBV group (368 (242)) (p<0·01). While the intensity of T8 antigen expression on suppressor cells was not significantly different in PBC (347 (125) 10⁴ cells) compared with NS (441 (206)), the mean proportion of CD8 positive cells was significantly less in PBC (% 14-1 (6-8)) than controls (% 20 (4-7) (p<0·05).

These data may suggest that the reduced suppressor cell number and function reported for PBC patients may be a consequence of the release of T8 antigen from these populations possibly due to lymphotoxin or anti-lymphocyte antibody, or both, seen in these patients.

**Endothelial cell transformation in primary biliary cirrhosis**

C BABB, N Y HAROUBI, M MULLOR, A SMITH, B P ROWAN, AND I W WARNES (Liver Unit, University Hospital of South Manchester) Endothelial cells (EC) lining normal hepatic sinusoids are characterised by the presence of cytoplasmic fenestrations, absence of a basal lamina, and lack of staining for factor VIII related antigen (FVIII RAg). In cirrhosis these cells may transform to vascular type ECs with deposition of a basement membrane and expression of FVIII RAg. These changes may lead to liver cell failure. The aim of this study was to look for morphological and biochemical evidence of EC transformation in 65 patients with PBC.

Liver biopsies, staged by the Ludwig criteria, were stained for FVIII RAg and the basement membrane components laminin and type IV collagen by an indirect immunoperoxidase technique (28 cases). Hyaluronic acid (HA), a glycosaminoglycan catabolised by normal sinusoidal ECs, was measured in serum by radiometric assay.

Sinusoidal ECs were negative for FVIII RAg in normal biopsies. Positive staining was seen occasionally in stage II PBC but was most noticeable in patients with cirrhosis at the interface of fibrous septae and parenchyma. These changes were accompanied by a clear increase in staining for laminin and type IV collagen. Serum HA concentrations were significantly higher in patients than controls (p<0·001) and correlated strongly with histological stage (p<0·001). Serum albumin (p<0·001) and bilirubin (p<0·001).

In conclusion, we have found morphological and biochemical evidence of EC transformation in patients with PBC. These changes are potentially important in disease progression by impairing nutrient transport to hepatocytes which may lead to the development of liver cell failure.

**Basement membrane markers and portal hypertension in primary biliary cirrhosis**

C BABB, A SMITH, V COPE, D SCHUPPAN, N Y HAROUBI, AND I W WARNES (Liver Unit, Manchester Royal Infirmary, Dept of Gastroenterology, Free University of Berlin, and University Hospital of South Manchester) Sinusoidal portal hypertension (PHT) is a common early feature of primary biliary cirrhosis (PBC), although the mechanisms remain uncertain. It has been suggested that changes to the sinusoidal endothelium with basement membrane (BM) deposition might contribute to this by increasing resistance to blood flow. Our aim was to study the relation between PHT and BM turnover in 65 patients with PBC.

Portal pressure was measured by hepatic
vein catheterisation (wedged-free = WHVPc). Presence of varices was assessed by endoscopy or barium swallow, or both (n=57). Type IV collagen (NCl) and laminin (Lam P1) were measured in serum by recently developed RIA s.

Raised serum values of NCI and Lam P1 were found in 75% and 59% of patients respectively: both correlated with histological stage (p<0.001). WHVPc was raised (>6 mmHg) in 87% of all cases, and in 80% (16 of 20) of those with early disease (stage I and II). WHVPc correlated with serum NCI (p<0.001) but less well with serum Lam P1 (p=0.02); no significant correlations were found in patients with cirrhosis or varices, or both. In many patients, Lam P1 and NCI values were normal despite established PHT.

In conclusion, in PBC, the early rise in WHVPc seems to precede increased serum values of BM markers. PHT may therefore be the cause of increased BM turnover rather than its consequence as previously postulated.

Immunohistochemical characterisation of the portal tract mononuclear cell infiltrate in chronic liver diseases of childhood

G Senaldi, A Lobo-Yeo, B Portmann, A PMowat, G Mieli-Vergani, and D Vergani (Depts of Immunology and Child Health and Liver Unit, King's College School of Medicine and Dentistry, London) The portal tract mononuclear cell infiltrate (MNCI) was analysed in 30 liver biopsy specimens from 11 children with autoimmune chronic active hepatitis (CAH), 12 with primary sclerosing cholangitis (PSC), and seven with other chronic liver diseases (CLD) (three with alpha-antitrypsin deficiency, two with Wilson's disease, one with HBV infection, and one with Alagille's syndrome) with the histological diagnosis of chronic aggressive hepatitis. MNCI was quantitated in a two-step immunoperoxidase technique using monoclonal antibodies to total (OKT3), a/b-TCR (WT31), T(b)-TCR (B72.3), helper/inducer (OKT4), suppressor/cytotoxic (OKT8) T lymphocytes, B (THB-5) and K/NK (B73.1) cells, monocyte/macrophages (OKM1) and to the activation markers HLA-DR, antigens (L243) and IL-2R (anti-TAC). In all conditions the infiltrate mainly comprised a/b-TCR T lymphocytes (60–90%), T(b)-TCR cells being absent, but whilst T helper/inducer predominated in autoimmune CAH, T suppressor/cytotoxic lymphocytes were preponderant in PSC and the other CLD. K/NK cells accounted for up to 25% of the MNCI in autoimmune CAH, being rare or absent in the other conditions. OKM1+ cells were always found, but they were more numerous in PSC than in the other CLD. B lymphocytes were rare or absent. In autoimmune CAH and PSC most cells of the infiltrate expressed HLA-DR antigens and up to 75% displayed the IL-2R, while in other CLD HLA-DR+ cells were less frequent and IL-2R+ cells were rare or absent. The cells responsible for the histological picture of chronic aggressive hepatitis vary in their functional phenotype and state of activation according to the type of the underlying liver disorder, confirming the involvement of different pathogenetic mechanisms.

Specific reactivity of a mitochondrial antibody in women with recurrent urinary tract infection against the PBC specific 70KD mitochondrial autoantigen, shown by immunopurification

A K Burroughs, P Butler, D Brown, W Brumfit, J Hamilton Miller, and H Baum (Academic Departments of Medicine and Medical Microbiology, Royal Free Hospital and Dept of Biochemistry, Kings College, London) We have shown that women with primary biliary cirrhosis (PBC) suffer from recurrent UTIs, and that PBC specific anti-mitochondrial antibody (M2) directed against the 70 KD peptide present in beef heart mitochondrial preparations, cross-reacts specifically with 70 KD and 50 KD peptides of urinary organs. Thus M2 antibody may be related to UTIs.

Using immunoblotting against mitochondria we tested sera of 30 women with documented recurrent bacteriuria without PBC, for the presence of M2 PBC specific antibody. Antibody against the 70 KD M2 antigen was present in 22 (73%) of patients. In addition, all sera also exhibited reactivity with a higher molecular weight band of 200 KD. After immunopurification the antibody to the 70 KD mitochondrial peptide cross reacted against both the 70 KD and 50 KD fractions of E coli, K pneumoniae, and P mirabilis. In 10 age matched normal controls there was no reactivity against the 70, 50, or 40 KD mitochondrial peptides and only reactivity against 200 KD peptides.

These findings suggest the M2 antibody in women with recurrent bacteriuria is not the previously reported naturally occurring mitochondrial antibody. As most cirrhotics have antibodies to E coli but do not have M2 antibodies our finding of M2 antibody in patients with recurrent bacteriuria suggests that a urinary route of infection may be important for the development of PBC specific M2 antibody.

Primary sclerosing cholangitis: prognostic value of symptom status, serum bilirubin, procollagen III peptide, and HLA phenotype

J A Snook, A Rudenski, R Herrmann, J D S Kay, J Dooley, N McIntyre, D P Jewell, and W G Chapman (Depts of Gastroenterology and Clinical Biochemistry, John Radcliffe Hospital, Oxford and Dept of Medicine, Royal Free Hospital, London) Primary sclerosing cholangitis (PSC) commonly runs a fluctuating and unpredictable course, and universally accepted prognostic markers have yet to be established. The aim of this study was to assess the prognostic value of symptom status, serum bilirubin, procollagen III peptide concentration, and HLA phenotype in a cohort of 46 patients with PSC who were initially diagnosed or under follow up during the period 1979–1983.

The overall eight year survival from the time of cholangiographic diagnosis was 69% (Kaplan Meier product limit technique). Thirty three per cent had experienced no symptoms of liver disease before diagnosis. Seven year survival was 100% for this group, compared with only 60% for those who had symptoms before diagnosis (p<0.01).

A raised serum bilirubin concentration at diagnosis was of no value in predicting seven years survival, but was found in all four patients who died from liver disease within two years. Procollagen III peptide concentrations were above the normal range in 42%, and correlated significantly with the degree of portal tract inflammation and fibrosis, but values were of no prognostic value. There was a non-significant trend towards poorer survival in B8 positive subjects. The results indicate that symptom status is of major prognostic significance in PSC.

Analysis of the pathological features of 40 cases of chronic liver transplant rejection

D G D Wight (Dept of Histopathology, Addenbrooke's Hospital, Cambridge) Chronic rejection of the transplanted liver (often referred to as vanishing bile duct syndrome) is the most important cause of graft failure beyond the initial postoperative period. A series of 40 cases has been analysed pathologically. Diagnosis was based upon full pathological examination of the whole liver either at retransplantation...
Propranolol does not adversely affect hepatic redox state or oxygen consumption in advanced alcoholic liver disease

P MCMATHUNA, P VLAVIANOS, C GROVE, J WENDON, D WESTABY, AND R WILLIAMS (Liver Unit, King's College Hospital and School of Medicine and Dentistry, London) The increasing use of propranolol (Prop) for the prophylaxis of variceal bleeding has raised the question of potential adverse metabolic effects in advanced alcoholic liver disease (ALD).

To investigate this in 10 patients with ALD (all Child-Pugh >B9), we assessed (a) hepatic redox state (HRS) indirectly by measuring the arterial ketone body ratio (KBR)—that is, ratio of acetacetate/β-hydroxybutyrate, and (b) systemic and hepatic oxygen delivery (DO₂) extraction ratio (%O₂E) and consumption (VO₂) together with full systemic and splanchnic haemodynamics, before and after intravenous Prop (0·1–2 mg/kg). Results are shown as mean (SD). Prop reduced DO₂ (700 (105) v 583 (103) ml/min/m², p<0·05). The %O₂E increased, however (18·5 (4) v 22·6 (5·2%), p<0·05), resulting in unaltered VO₂ (127 (23) v 131 (22) ml/min/m², p=0·01). Similarly hepatic VO₂ did not change. Basal KBR (0·44 (0·25)) was within normal limits (0·51 (0·06) derived from a cohort of subjects with normal liver function) was unchanged by Prop (0·44 (0·25) v 0·48 (0·22)) and in fact improved in two patients (Child C 12 and 13) from 0·17 to 0·34 and 0·18 to 0·27, respectively.

In conclusion, Prop does not compromise %O₂E or VO₂ in advanced ALD, despite reducing DO₂ and does not adversely affect HRS, as reflected by KBR, which may indeed improve in some patients. The results support the safety of Prop in advanced ALD.

Is the baboon a model for human alcoholic liver disease?

A J TURNBULL, C CAINLEY, I M H BROWN, D R DAVIES, C A HES, B M SLAVIN, W D MITCHELL, P W KEELEING, AND R P THOMPSON (Gastrointestinal Lab, Depts of Diabetics, Chemical Pathology, and Histopathology, St Thomas's Hospital, London, and St James's Hospital, Dublin) Fatty liver, alcoholic hepatitis, or cirrhosis, or both, have been described in all baboons fed alcohol with the Leiber-De Carli (L-DC) liquid diet for up to four years. We have previously found little change in the livers of baboons on a nutritious semisolid diet, containing alcohol, for five years. Thus, to clarify the role of nutrition we have now given alcohol for 38 months to four female baboons on the L-DC diet. The alcohol content was progressively increased to 16 g/kg body weight/day (60% of total calories). Animals were monitored by weighing, liver blood tests, blood ethanol values, and liver histology.

All animals gained weight slowly for 32 months but then lost weight. Blood ethanol concentrations two hours after feeding were 225–472 mg%. At 38 months, mean concentrations of alanine and aspartate aminotransferases and γ-glutamyl transferase were normal. Liver histology was normal in two animals and showed mild fatty change in two. None had alcoholic hepatitis or abnormal liver architecture.

We are still unable to confirm the hepatotoxicity of alcohol in the baboon, despite accompanying suboptimal nutrition. Perhaps a specific dietary component is needed to exacerbate the toxicity of alcohol.

Increased neutrophil membrane w-3 fatty acids may be of clinical benefit in ulcerative colitis

A BELLUZZI, A R HAWTHORNE, T K DANISHMEND, AND T J HAWKEY (Dept of Therapeutics, University Hospital, Nottingham) Fish oil supplements in colitis (UC) suppress neutrophil (PMN) LTB₄ production. To further investigate this we studied PMN and rectal biopsy phospholipid fatty acid profiles by thin layer chromatography and gas chromatography. In patients on fish oil (4·5 g EPA daily) (n=seven), EPA content of PMN phosphatidylethanolamine (PE) was 6·6% v 1·4% (p<0·01) in patients taking olive oil placebo (n=six). The EPA/araachidonic acid (AA) ratio was 0·78 v 0·12 (p<0·001). In phosphatidylincholine (PC) EPA content was 1·9% v 0·6% (p<0·05). The EPA/AA ratio 0·75 v 0·16 (p<0·05). Similar changes were observed in rectal mucosa with the EPA/AA ratio 0·5 v 0·16 (p<0·05). An interim safety analysis in the trial at six months showed that on fish oil, 37 patients had a median
30 patients on placebo 100/180 (IQR 0–165) (p<0.15). For those entering the trial in remission there was a tendency for lower steroid use: five of 16 patients on fish oil required prednisolone, median 200 mg (range 186–1000), and five of 11 on placebo took 810 mg (430–4736).

There is no evidence of toxicity and increased w-3 fatty acids in PMN phospholipids shows promise of a clinical benefit in ulcerative colitis.

Eicosapentaenoic acid in chronic ulcerative colitis

A Tobin, Y Suzuki, and C O Morain (Meath and Adelaide Hospitals, Trinity College, Dublin) Ingestion of fish oil reduces production of lipid derived inflammatory mediators implicated in inflammatory bowel disease, possibly by eicosapentaenoic acid (EPA) inhibition of arachidonic acid metabolism.

Twenty three patients with chronic ulcerative colitis (UC) entered a double blind, crossover trial comparing four months of pure EPA with four months of corn oil placebo, separated by a six week washout. Patients were assessed clinically at monthly intervals. Colonoscopy was performed before and after the first treatment, and at the end of the second treatment. Study end points were completion of treatment or deterioration requiring high dose oral steroids or hospital admission. Maintenance medications were continued. Improvement by at least one grade of at least one of five parameters (well being, pain, bleeding, mucus, bowel frequency) was considered to be a successful outcome.

Thirteen patients received EPA as their first treatment; 10 improved, two were unchanged, and one became worse. Ten patients received corn oil first; three improved, five worsened, and two remained unchanged. Improvement was sustained throughout the washout and corn oil treatment in five of the 10 who improved on initial EPA. Three of the seven patients who did not improve on corn oil improved during subsequent EPA treatment.

This study suggests that EPA may be useful in chronic active UC.

Plasma interleukin 2 receptor values in inflammatory bowel disease

Y R Mahida, A Gallagher, and C J Hawkey (Dept of Therapeutics, University Hospital, Nottingham) Activated T cells produce interleukin 2 and express specific receptors (IL2R) for this cytokine. We measured IL2R values in plasma of normal subjects (n=15) and patients with active ulcerative colitis (UC) (n=11) and Crohn’s disease (n=11).

Plasma was obtained from venous blood by centrifugation and samples were stored at −7°C until assayed for IL2R using ELISA. Results are expressed as mean (SEM) IL2R U/ml.

IL2R values correlated with score of activity (r=0.68; p=0.011), values of C-reactive protein (CRP) (r=0.9; p=0.02), and ESR (r=0.67; p=0.018). Highest values were detected in plasma from peripheral and mesenteric venous blood from a patient with toxic megacolon. The IL2R values were raised in active Crohn's disease in four patients with a normal ESR, four with normal CRP, and three with normal oesomucoid values. In a Crohn's patient, IL2R concentrations fell on clinical response to corticosteroids.

Plasma IL2R values correlate with disease activity in UC and may be of value in assessing activity of Crohn's disease.

Increased pulmonary permeability in Crohn's disease

A Adenis, P Lehouffer, J F Colombel, B Wallaert, X Marchandise, and A Cortot (Clinique des Maladies de l’appareil digestif, Service associé de Médecine nucléaire et Dépt de Pneumologie, Centre Hospitalier Universitaire Lille, Cedex, France) An increased intestinal permeability (IP) has been described in Crohn's disease (CD).

We tested the hypothesis that this abnormal permeability may not be confined to the intestine by evaluating pulmonary permeability (PP) in patients with CD.

Pulmonary permeability and IP were measured in 10 patients (age 21–43 years) with active CD (CDAI>150). Five and six had second evaluations of PP and IP respectively when quiescent. Eleven (for IP) and 15 (for PP) healthy volunteers (age 21–43 years) served as controls. Patients and controls were non-smokers and had no pulmonary symptoms. Pulmonary permeability was measured by the t½ clearance of a micronebulised (0.8 μ) aerosol of "°TeDTPA. IP was evaluated by the °CrEDTA test.

The IP was increased – that is t½ decreased, in active CD, mean (SD) 53.5 (15.9) min v controls 105.6 (35.7) min (p<0.002) but did not differ between active and inactive CD. The IP was increased in active CD (7-9 (6-8%) v controls 2 (1-3%) (p<0.001) and was higher in active (7-8 %) v inactive CD (2-6%) (p<0.04). No correlation was found between IP and PP.

We conclude that: (a) In active CD, PP, and IP were increased. (b) Unlike IP, PP was not influenced by CD activity. (c) These data suggest a diffuse increased mucosal permeability in CD.

Cigarette smoking and recurrence rates in Crohn's disease

The British Society of Gastroenterology
Effect of smoking on rectal mucosal blood flow

E D SRIVASTAVA, M A H RUSSELL, C FEYERABEND, AND J RHODES (Dept of Gastroenterology, University Hospital of Wales, Cardiff and The Addiction Research Unit, Institute of Psychiatry, London) Ulcerative colitis (UC) is associated with non-smoking. Smoking may alter rectal mucosal blood flow (RMBF) which may in turn influence susceptibility to colitis. RMBF was measured for 60 minutes by laser doppler flowmetry with an angled probe (Periflux PF2, PF110 angle probe, Perimed) in 10 healthy male smokers, eight non-smokers, and eight patients with distal UC in remission. Each smoker had two sets of measurements: one while smoking a cigarette at 30 minutes, and on another occasion without smoking. Smokers had not smoked for two hours before the test. Blood was taken to measure nicotine concentrations. All four groups of results showed an appreciable fall in RMBF over the first 30 minutes. Patients with UC had a higher RMBF compared with smokers (p<0.002; p<0.04), and non-smokers (p<0.007; p<0.002) during the first and second 30 minutes of the test respectively. There was an inverse correlation between the rise in nicotine concentration and the fall in RMBF in smokers (r = -0.69; p<0.05). The RMBF between 30 and 60 minutes was significantly lower in the smokers when they had a cigarette (p<0.04). There was no difference between smokers, smoking, and non-smokers. Smoking causes a transient reduction in the RMBF and may modify the patient’s susceptibility to UC.

Effects of elemental diet on the faecal flora in patients with Crohn’s disease

M H GIFFER, C D HOLDSWORTH, AND B J DUERDEN (Dept of Microbiology, University of Sheffield and Gastroenterology Unit, Royal Hallamshire Hospital, Sheffield) Alteration of faecal flora has been suggested as a possible mechanism by which elemental diet exerts its therapeutic effects in Crohn’s disease. Faecal flora were studied in 13 patients with active Crohn’s disease who were receiving an elemental diet (Vivonex) as the only treatment. Stool samples were collected before and at weekly intervals after the start of Vivonex: 1 g wet weight was diluted in 9 ml of phosphate buffered saline, pH 7.2, and plated by a standard method on blood agar, MacConkey, Reinforced Clostridial Cotton blue, Rogosa, Sabouraud and Bacteroides isolation agars which were incubated aerobically or anaerobically. The plating method was calibrated by comparison with a conventional surface viable count and gave a reliable semiquantitative assessment of faecal micro-organisms. All isolates were identified by routine bacteriological methods. Counts of total anaerobic bacteroides, bifidobacteria, and clostridia were not significantly changed, and neither were total aerobic and E coli counts. The number of aerobic and anaerobic species isolated also remained unchanged throughout. The mean anaerobic lactobacillus counts decreased significantly in nine patients (70%) and in seven of them the organism disappeared completely from the stools. This change in lactobacilli count was observed within one week of starting Vivonex and was not related to any changes in the clinical condition of the patients.

These results suggest that alteration of faecal flora does not account for the beneficial effects of an elemental diet in Crohn’s disease.

Increased prevalence of inflammatory bowel disease (IBD) among family members of Greek IBD patients

D G KARANAMOUL, A ADAMOPOULOS, B XOURGAS, M XENOPHONTOS, S POURNARAS, AND A AVGARIDOS (Dept of Gastroenterology, Tzanion General Hospital, Piraeus and B’ Department of Gastroenterology, Evangelimos General Hospital, Athens) No data are available about familial patterns of inflammatory bowel disease (IBD) in Greece. To clarify this point, we studied the prevalence of known IBD cases among first and second degree relatives of 73 patients consecutively seen at our IBD outpatient department. Forty nine patient’s with ulcerative colitis (UC) and 24 with Crohn’s disease (CD) were studied. The family pedigrees of the 73 index cases included 384 first degree and 1661 second degree relatives. Six index cases (8.2%) showed a positive family history for IBD with eight relatives affected (six with UC and two with CD). The overall prevalence of IBD among relatives was therefore: 39/10 (293/10 for UC and 98/10 for CD). In first degree relatives the prevalence was 156/2 (UC=130/10 and CD=24/10) while it was only 120/10 (UC=60/10 and CD=60/10) in second degree relatives.

The prevalence of UC among first degree relatives of UC patients was 197/10; while that of CD among first degree relatives of CD patients was 763/10.

In conclusion we found high prevalence of IBD among first degree relatives, with second degree relatives being at a risk similar to that of the normal population.

Incidence of inflammatory bowel disease in the Nord-Pas de Calais region of France

J F COLOMBEL, J L SALOMEZ, A CORTOT, J L DUPAS, B LEMAIRE, P CZERNICHOW, E LEBEBOURS, AND J C PARIS (Clinique des Maladies de l’Appareil Digestif et Service d’Epidemiologie CHU Lille, Clinique Medicale A, CHU Amiens, Service d’Information Medicale et Service de Gastroenterologie CHU Rouen) No epidemiological data on inflammatory bowel disease (IBD) are available in France. Therefore we conducted a prospective
epidemiologic study of IBD in the region Nord-Pas de Calais (3·9 million inhabitants). Each new suspected case was reported by all (private and public) gastroenterologists (GE) in the region (n=104) and a questionnaire was filled up at the GE office by an epidemiologist. The final diagnosis of Crohn’s disease (CD), ulcerative colitis (UC), or proctitis was made in a blind manner by two expert GEs according to Calkins et al. During 1988, 500 IBD patients were identified; 239 (48%) had CD, 183 (37%) UC (including 65 proctitis); and 78 (15%) had unclassified colitis. The incidence rate (per 10^5) was 6·1 for CD and 4·7 for UC. The female/male ratio was 1·41 for CD and 0·85 for UC. The mean age at the time of diagnosis was 31 years for CD and 40 years for UC. The mean time between onset of symptoms and diagnosis was longer for CD (17 months) than for UC (6·8 months).

These preliminary data suggest that incidence of IBD is high in Northwestern France, especially for CD.

Ulcerative colitis and pregnancy in north east Scotland – a community study

M Hudson, G Fleet, I Sinclair, and NAG Mowat (G1 Unit and Dept of Obstetrics, Aberdeen Teaching Hospitals) There are few studies of the mutual effect of ulcerative colitis (UC) and pregnancy. We studied this relation in all 278 women with proved UC, aged 16 to 45 years, in NE Scotland during 1967–86. Data were derived from the centralised records department and from a detailed questionnaire to which we received 232 replies. Of these, 93 had completed their family before the onset of UC. Twenty had total colectomy and were studied separately. Of 118 potentially fertile women, 85 (72%) conceived on 160 occasions. Only seven (5·9%) had involuntary infertility. A total of 127 live births (including two premature), 18 spontaneous abortions, 14 ‘social’ terminations and one ectopic pregnancy were recorded. No congenital abnormalities or stillbirths occurred. Disease activity had no effect on the outcome of pregnancy. Of those with normal live births, 92 were in remission at conception but 29 (31·5%) relapsed during pregnancy. Of 20 with active UC at conception, 10 went into remission, eight were unchanged and two deteriorated. Ten patients had their first attack of UC in pregnancy and five in the puerperium. Salazopyrin, topical or systemic steroid did not increase the risks for baby or mother. Fertility in UC patients is not impaired.

UC runs a benign course in pregnancy, and neither disease activity or medical treatment affect the outcome.

Arthritis associated with Crohn’s disease

JMG Illyvarry, F Keeling, O Fitzgerald, and JF Fielding (Dept of Medicine, Beaumont Hospital, Dublin) This report describes the incidence of peripheral arthritis, sacroiliitis, ankylosing spondylitis and hypertrophic osteoarthropathy based on a prospective study of 55 patients with Crohn’s disease, and the relation of these arthropides with disease activity and HLA B27 status. It also compares their incidence with that of an age and sex matched control population. This is the first such prospective study. Peripheral arthritis occurred in eight (14·5%) of the 55 patients but in none of the 55 controls. The arthritis, which tended to be pauciarticular, was more common in women, in those with large bowel disease, and post dated the bowel symptoms in all but one patient. There was a close correlation with disease activity.

Radiographic sacroilitis occurred in seven (12·7%) and ankylosing spondylitis in four (7·3%) of the patients; neither of these were seen in the controls. Sacroiliitis was asymptomatic, more common in women, and showed no correlation with disease activity or HLA B27. Ankylosing spondylitis was seen equally in men and women, and showed close correlation with disease activity and HLA B27.

Hypertrophic osteoarthropathy was seen in five (9%) patients. It was not seen in the control group. All patients were asymptomatic and showed no correlation with disease activity, age of onset of disease, clubbing, or HLA B27.

Whereas the incidence of peripheral arthritis and sacroiliitis are comparable with previous reports, that of ankylosing spondylitis is higher than in all but one other series. This first prospective report of hypertrophic osteoarthropathy in Crohn’s disease suggests that its incidence is much higher than previously thought.

Improving quality of care in gastroenterology outpatients

W R Burnham, K Anderson, S J Day, R Oxner, J Nightingale, and S Squire (Dept of Gastroenterology, Oldchurch Hospital, Romford) Patients may misunderstand information from doctors; discussion with a gastroenterology nurse specialist or information leaflets may help. To assess this, 101 patients due to undergo endoscopy, 99 with barium enema, and 120 with inflammatory bowel disease (IBD) were interviewed by a research sister. Baseline understanding of the investigation or illness was scored. Patients were then randomised to no further information (group A), leaflet alone (group B), or leaflet plus counselling from nurse specialist (group C). At the next visit, tolerance of investigations or understanding of disease were scored.

All three groups tolerated endoscopy well, but B and C tolerated barium enema significantly better than A (p<0·005 Mann Whitney test). There was no correlation between prior understanding and tolerance of barium enema in A and no significant difference in tolerance between B and C.

Understanding of IBD was greater at second visit in B and C than A (p<0·02); C was not significantly greater than B (p=0·33) but only the nurse specialist detected important and unsuspected problems in 16% of patients. Information leaflets and nurse specialist improves quality of care in gastroenterology outpatients; benefit may not be due simply to better understanding.

LIVER II

Detection of measles virus by the reverse transcriptase polymerase chain reaction in the liver of patients with autoimmune chronic active hepatitis

DP Jackson, JI Wyatt, FL Lewis, DA F Robertson, GR Taylor, GH Millward-Sadler, MF Dixon, and P Quirke (Depts of Pathology, University of Leeds, St James’s University Hospital and University of Southampton, Dept of Medicine, University of Southampton, and DNA Laboratory, Leeds General Infirmary, Leeds) Autoimmune chronic active hepatitis (AICAH) is associated with high titres of antibodies against measles virus. A mechanism of persistent infection by defective measles virus may trigger an immunological response that results in AICAH. We have therefore investigated the presence of measles virus in the liver by the use of reverse transcriptase polymerase chain reaction (RT-PCR).

Nucleic acid was extracted from two paraffin embedded blocks of liver from a 12 year old girl with AICAH and analysed by RT-PCR using two oligonucleotide primers to amplify a 194 base sequence of the nucleocapsid region of the measles virus. DNA electrophoresis yielded a 194 base sequence. The British Society of Gastroenterology
bp DNA band from both blocks indicating the presence of measles virus. Liver biopsy material from three of four patients with CAH also contained measles virus.

Positive controls included two different measles vaccines and a measles nucleocapsid gene cDNA. Negative controls of distilled water were consistently negative.

The detection of measles virus by RT-PCR in AICAH provides a method to further investigate the precise nature of the relation (whether causal or not) between the virus and the disease.

Hepatitis in a HIV positive population

D P Nunes, K C Trimbale, A Shatlock, F M Mulcahy, and D G Weir (Depts of Clinical Medicine, Trinity College Dublin and St James’s Hospital, Dept Medical Microbiology, University College, Dublin) A combined prospective and retrospective study of 209 HIV positive outpatients (male 162; female 47) has been carried out since January 1988. Evidence of hepatitis was sought in 161 intravenous drug abusers (IVDA), 33 homosexuals (HS), eight heterosexual contacts, and two haemophiliacs: average age 26 years. Serological data for hepatitis B virus (HBV) was available in 153 and liver function tests in 196. Altogether 120 (61%) had evidence of biochemical hepatitis. Seventy nine of 93 (85%) had markers of past HBV infection (anti-HBc IgG), but only 10 (7%) were HBsAg positive. Three patients were HBcAgM positive indicating a low incidence of viral activity. No patient had documented acute HBV. Delta exposure was noted in 22 (all IVDA), chronic delta in three. Twenty of 47 (43%) had evidence of chronic hepatitis, and in eight this was confirmed on liver biopsy. In 10 patients a drug related hepatitis was identified. We have found no evidence of hepatitis related to opportunistic infections. No significant difference in the prevalence of hepatitis (IVDA 47%, HS 25%, p=0.08) or the incidence of past exposure to HBV (IVDA 87%, HS 73%, p=0.6) between the two major risk groups was seen. There was no apparent relation between CDC classification and the prevalence or severity of the hepatitis observed. The rate of HBV clearance in this group approaches that of the general population. As a minority of the hepatitis was HBV related a non-A non-B agent is proposed as the aetiology in the majority.

Haemodynamic and hormonal influences in cirrhosis with and without ascites

P C Hayes, A D Cumming, and I D Bouchier (Dept of Medicine, Royal Infirmary, Edinburgh) Many haemodynamic and biochemical changes have been recorded in isolation in cirrhotic patients with ascites, most noticeably a rapid renal sodium retention. The pathophysiology, however, remains poorly understood. The purpose of the investigation was to study the combination of haemodynamic and hormonal changes including the involvement of the renal kallikrein (natriuretic) system, in six patients with histologically proven cirrhosis with untreated ascites and six without ascites on no diuretic treatment.

The following haemodynamic measurements were made: portal pressure, right atrial and ventricular pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, renal sodium blood flow, and glomerular filtration rate. Biochemical investigations included urinary sodium and kallikrein, plasma renin, prekallikrein, aldosterone, angiotensin II, atrial natriuretic peptide, adrenalin, and noradrenalin. No significant differences were found between the ascitic and non-ascitic groups except for the rate of urine production, sodium excretion, angiotensin II, and the plasma renin/urinary kallikrein ratio. With respect to sodium excretion, no parameters correlated except for the plasma renin-urinary kallikrein ratio (r=0.8, p<0.002). This ratio, a measure of the balance of natriuretic and salt retaining factors correlates so strongly with sodium excretion in this and other pathological states that it implies causality in the genesis of sodium retention.

Natural history and prognostic variables in primary sclerosing cholangitis

J M Ferranti, K M Hayllar, M Wilkinson, G J M Alexander, D Westaby, and R Williams (Liver Unit, King’s College Hospital and School of Medicine and Dentistry, London) Primary sclerosing cholangitis (PSC) is a disease of unknown aetiology for which no proved treatment is available. There is controversy concerning prognosis and whether there are clinical features which are related to survival. To investigate this further, we retrospectively reviewed 124 patients with PSC (median follow up 5-85 years, range 2 months–12-5 years). Sixty three per cent were male, median age at presentation was 35 years (range 3-70), median survival 12.7 years, 10 year survival was 61%. Ulcerative colitis was present in 79 patients (69%), the diagnosis clearly preceding PSC in 54, and clearly following PSC in 11. Forty six patients died or were transplanted (22 deaths, median 6 years, range 3 months–18 years; 24 transplants, median 7-8 years, range 1 year–22 years). Using Cox regression analysis with log transformation of bilirubin and alkaline phosphatase concentrations, hepatomegaly, serum bilirubin, and serum alkaline phosphatase were associated with decreased survival: sex, presence of symptoms, inflammatory bowel disease, serum albumin, cirrhosis, and HLA phenotype were not. We confirm that PSC is progressive; 37% of our patients have died or been transplanted. The prognostic features that we have identified confirm previous findings, but we disagree with a recent report that inflammatory bowel disease is an independent prognostic indicator.

Prolonged survival in hepatocellular carcinoma patients after anti-oestrogen treatment

F Farinati, S Fagiuolo, L Rossaro, M Salvagnini, M Chiaramonte, and R Naccarato (Cattedra Malattie Apparato Digerente, Istituto di Medicina Interna, Policlinico Universitario, Universita’ di Padova, Italy) Clinical and experimental evidence suggests a correlation between oestrogens and the development of hepatocellular carcinoma (HCC) and it has been shown that liver regeneration after partial hepatectomy is an oestrogen controlled process, largely inhibited by tamoxifen administration. In a prospective, controlled, therapeutic trial, 28 consecutive cirrhotic patients with unresectable HCC were allocated to either 30 mg/die tamoxifen or no treatment. The two groups of patients were matched for age, male/female ratio, Child-Pugh risk group, and approximate tumour mass. No adverse effects of the drug were observed. The difference in survival between the two groups, determined by life table analysis (generalised Wilcoxon-Breslow test) was statistically significant (p<0.001), with 40% v 0% survival at 12 months in the two groups. In 45% of the tamoxifen treated patients, an initial reduction in α fetoprotein values was observed. On the other hand, LDH, alkaline phosphatase values, and tumor mass increased in the large majority of the patients, suggesting a continuous but slower progression of the disease.

In conclusion, anti-oestrogen treatment seems to be effective in the palliative treatment of unresectable HCC.
Growth response of hepatocellular carcinoma cells to oestrogens in culture is critically concentration dependent

A A SANTOS, A STUBBS, S E J EDMUNDS, AND M I WILKINSON (Gastroenterology Unit, United Medical and Dental Schools, Guy’s Campus, London) The relation between sex-steroids and the aetiology and growth of hepatocellular carcinoma (HCC) is controversial. Oestrogens have often been implicated in the aetiology of this tumour, mainly from experiments in rodents. In addition, oestrogens cause regeneration of normal liver in hepatectomised rats. The aim of the present study was to examine the effects of 17-α-ethinylestradiol (EE2) on cell proliferation (DNA) and protein production (albumin and fetal steroid binding protein: FSBP) in a human HCC-derived cell line, HepG2.

Cells were cultured in Dulbecco’s supplemented with 10% fetal calf serum and Phenol Red (PR). The medium was changed to Dulbecco’s without PR (serum free medium: SFM) for 48 hours and then incubated in SFM with EE2 at seven concentrations (0.5, 5, 50, 500 nM). After 48 hours medium was assayed for FSBP and albumin by ELISA. DNA was measured by spectrophotometry. There were six results.

Production of FSBP and albumin was not significantly affected by EE2. The value of DNA per plate decreased from 0.384 mg (0 nM) to 0.263 mg at 0.5 nM (p=0.001) and 0.261 mg at 5 nM (p=0.009).

Ethinylestradiol dramatically inhibited growth at 0.5 and 5 nM but there was no effect on protein secretion at any steroid concentration tested. These results contradict suggestions that oestrogens are promoters of HCC in man. The reasons for the differences from results in rats are not clear.

Randomised trial of longterm sclerotherapy for variceal rebleeding using the same protocol to treat rebleeding in all patients.

Final report

A K BURROUGH, P A MCCORMICK, S SIRINGO, A PHILLIPS, D SPRENGER, AND N McINTYRE (Academic Dept of Medicine and Clinical Epidemiology, Royal Free Hospital, London) All randomised controlled trials of longterm sclerotherby, except one, have used emergency sclerosis in the sclerotherapy but not in the control group, thus evaluating both acute and chronic injection v none. As acute injection reduces early rebleeding and mortality compared with conventional therapy, the beneficial effect of chronic injection may be overestimated. During 62 months we randomised, 204 cirrhotics with bleeding oesophageal varices to weekly sclerotherapy (n=103) or no injection (n=103) and the latter were given sucralfate 1 g daily. A standard protocol was used to treat all bleeds, and randomisation took place after a five day bleed free interval from admission stratified by the initial treatment used. Trial groups were well matched, including Pugh’s grades A, B, C (sclerotherapy 35; 42, sucralfate 22; 17: 24). Deaths: 55 (53%) sucralfate and 48 (47%) sclerotherapy (log rank p=0.49). Oesophageal and gastric variceal rebleeding occurred in 59% sucralfate v 55% sclerotherapy patients (log rank p=0.46). Total number of variceal rebleeds (unknown sources were considered varical) were 183 sucralfate and 130 sclerotherapy. In each trial group 3% had transplants, 7% had shunts, and 1% had devascularisation.

Longterm sclerotherapy does not significantly benefit patients when emergency treatment for bleeding is kept constant. The reduction in variceal rebleeding episodes is marginal; 50 episodes for 100 patients treated over five years.

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Endoscopic retrograde pancreatography in the surgical management of chronic pancreatitis

P E JENNINGS, S N JONES, W R LEES, R C G RUSSELL, AND A HATFIELD (Middlesex Hospital, London) Altogether 132 patients with a clinical diagnosis of chronic pancreatitis, who had endoscopic retrograde pancreatography (ERP) before pancreatic resection were retrospectively reviewed.

The ERP findings were recorded using the modified ‘Cambridge’ classification of chronic pancreatitis. The surgical and histological appearances were similarly graded according to severity of disease. The aetiology of the chronic pancreatitis and symptomatology were recorded for all cases. Symptomatology was assessed on a five point scale ranging from pain free with a normal lifestyle to severe pain requiring opiate analgesia.

The ERP findings correlated with surgical and histological appearances in 90% of cases. ERP predicted the extent of surgical resection required in all these cases (vis: Whipple v distal pancreatectomy v total pancreatectomy).

The 10% with poor correlation were due to an underestimation of the severity of disease by ERP. A subgroup was identified in whom ERP, surgical, and histological findings showed good correlation but surgical outcome was poor. This group may represent a hitherto undescribed disease process.

Tissue diagnosis of abdominal masses using ultrasound guided biopsy

N COUSE, H JAEGEIR, D WAI, J MACIE, AND C J MITCHELL (Scarborough Hospital, Scar-
of fine needle aspiration cytology are well recognised.Further, biopsy using large gauge needles is potentially hazardous and, particularly with regard to abdominal masses, is unreliable. Percutaneous ultrasound guided biopsy (PC-US-By) using a Biopsy gun provides adequate histological samples but the safety and accuracy of the method is unknown. This study reports our experience using PC-US-By in 84 patients aged 16–82 years. Biopsy failed in five (6%) patients. Adequate histological samples were obtained in the remaining 79 (94%) patients. Of these, 36 had pancreatic, 22 liver, and the remaining 21 undiagnosed abdominal masses. Follow up was continued until death or confirmation of diagnosis. There were no serious complications. Malignancy was diagnosed in 52 patients (25 pancreatic, 13 liver, 14 abdominal) in 18 of whom confirmation of dissemination obviated the need for further investigation. A pre-biopsy diagnosis of gastrointestinal malignancy was correctly changed after PC-UC-By in 25 patients, of whom 19 had benign disease resulting in important changes in clinical management. There were no false positive and two false negative results in this series.

We conclude that PC-US-By of abdominal masses is a safe and accurate method of obtaining histological diagnosis and significantly influences clinical management.

Are serum values of tumour markers useful clinically in predicting the presence of pancreatic malignancy?

J K RAMAGE, R Iorns, D A F Robertson, C Alvyn, and D G Colin-Jones (Royal Naval Hospital, Haslar; Queen Alexandra Hospital, Portsmouth; and Southampton General Hospital, Southampton, Hants) Previous studies of the serum tumour markers CA19/9 and CEA have shown separation between pancreatic cancer and benign pancreatic diseases on retrospective analysis. To assess whether these markers are useful in clinical practice, serum samples were taken from 124 patients referred for endoscopic retrograde cholangiopancreatography (ERCP). Assays of CA19/9 and CEA were performed using the commercially available RIA kits. Altogether 111 patients (26 malignancies, seven with chronic pancreatitis, and 78 with benign disease) were diagnosed on the basis of clinical, ERCP or surgical findings, or both, with follow up (one to six months). A cut off of 95 U/ml (CA19/9) and 5 ng/ml (CEA) was used. CA19/9 was 96% sensitive and 87% specific in detecting pancreatic malignancy compared with all other conditions, and overall accuracy was 89%. For CEA, sensitivity and specificity were 72% and 80%. Ultrasound reports before ERCP predicted cancers correctly in 78%, were incorrect in 5%, and inconclusive in 17%. CA19/9 was 90% accurate in discriminating cancer from chronic pancreatitis.

Serum values of CA 19/9, in contrast with CEA values, compare favourably with ultrasound in detecting patients with pancreatic malignancy and will prove to be clinically useful.

Diagnostic and therapeutic endoscopic retrograde cholangiopancreatography in patients after Billroth-II gastrectomy — a review of 162 consecutive patients

S J WILLIAMS, J F Dowsett, A R W Hatfield, C C Ainley, and A C Smith (Dept of Gastroenterology, The Middlesex Hospital, London) The success rate of endoscopic pancreateobiliary procedures in patients with a Billroth-II (B-II) gastrectomy has varied widely in reported series. We report the success of endoscopic retrograde cholangiopancreatography (ERCP) performed at a tertiary referral centre during the last six years in 162 consecutive patients (131 male, 41 female, mean age 69 years [30–90]) with a B-II gastrectomy. Indications for ERCP included suspected common bile duct (CBD) stones (65), diagnosis of pancreatic (41), or biliary disease (20), and obstructive jaundice (36). Side viewing duodenoscopes were used in 112 patients, endviewing gastroscope in 16 patients, and a combination in 34. Intubation of the afferent loop was usually performed under x-ray control and aided by previous insertion of an 05 guidewire into the afferent loop.

Successful diagnostic ERCP was performed in 109 (67%). Failures were due to inability to negotiate the afferent loop or find the papilla (32), failed cannulation (11), tumour invasion of afferent loop (10). Sphincterotomy for CBD stones was successfully performed in 37 of 45 attempts (82%) using a conventional papillotomy (20 patients), a sharks fin papillotomy (five), or a needle knife (12). In eight patients, pigtail stents were inserted for incomplete clearance of CBD stones. Stent insertion for malignant biliary obstruction was successful in eight of 18 attempts; in five cases a combined percutaneous/endoscopic technique was used. Failed stents were due to tumour invasion adjacent to the papilla (six) and inability to negotiate the stricture (four). Procedure related complications occurred in six – bleeding three, choledangiitis one, retroperitoneal perforation one, and afferent loop perforation one.

We conclude that: (1) Diagnostic and therapeutic ERCP is less successful in patients with a B-II gastrectomy. (2) Negotiation of the afferent loop or sphincterotomy, or both, may be helped by the use of both end viewing and side viewing endoscopes and the use of the sharks fin papillotomy or needle knife. (3) In malignant biliary obstruction, a combined percutaneous/endoscopic procedure is often needed for stent insertion.

Obstructive jaundice with stones in the gall bladder: a trap for the unwary

R I HALL, C J H Ingoldby, and M E Denyer (Depts of Surgery and Medicine, St James’s University Hospital and Seacroft Hospital, Leeds) Patients with obstructive jaundice are frequently shown to have gall bladder stones and dilated ducts by ultrasound. We have examined whether these findings are adequate to allow surgery without further investigations. A total of 94 jaundiced patients with ultrasonic biliary dilation underwent endoscopic retrograde cholangiopancreatography (ERCP). Some 35 patients had previously undergone cholecystectomy and 59 had not. The final diagnoses were confirmed by cholangiography, biopsy, or operation.

Ultrasound specified the nature of biliary obstruction in 37 patients (37%), the level in 40 (42%), and was incorrect in 17 (18%). Retrograde cholangiography was successful in 92 patients. Malignant obstruction was much more common in patients with intact gall bladders than in those who had had cholecystectomy (39 vs 11%, p<0.01). Even when stones were present in the gall bladder malignant disease remained as common a cause of jaundice as calculus obstruction (33% vs 36%). The frequency of choledocholithiasis was greater after cholecystectomy than in patients with gall bladders (69% vs 30%, p<0.01). A similar proportion of each group had miscellaneous causes of jaundice.

The unexpected frequency of malignant obstruction in patients with intact gall bladders, together with the potential for endoscopic therapy, suggest that ERCP should be considered in all patients with obstructive jaundice.
Percutaneous cholecystolithotomy - an alternative to cholecystectomy?

C AINLEY, S N JONES, A C SMITH, A R W HATFIELD, W R LEES, R C G RUSSELL, J A INGLIS, M KELLETT, AND J WICKHAM (Dept of Gastroenterology, The Middlesex Hospital, London and The Institute of Urology, London) The results of cholecystectomy are satisfactory, but gall stones may be treated by less invasive methods. We report the results of 65 consecutive patients treated by percutaneous cholecystolithotomy (PCL) in two centres. Six patients had cholecystostomy tubes in situ as treatment for gall bladder (GB) empyema, and 59 were either reluctant or unfit for surgery. Suitability for PCL was determined by ultrasound (US). Under general anaesthetic, PCL was carried out after US guided GB puncture. After PCL, a Foley catheter was left in situ for 10 days.

Percutaneous cholecystolithotomy was successful in 58 patients (89%). There were four failures of GB puncture and in two patients after puncture the GB was not distensible. All six had cholecystectomy. Direct extraction with or without a basket was carried out in 26 patients, and 24 required electrohydraulic lithotripsy (EHL). The other nine had combinations of US, EHL, and laser lithotripsy. Nine patients had repeat PCL for retained GB stones. but one patient with a retained stone impacted in Hartmann's pouch required cholecystectomy. Mean in patient stay was 7-2 days (range 3-24). Ten patients (16-9%) had complications which included: bile leak (six); bowel puncture (three); and pancreatitis (one). These were managed conservatively, apart from one patient with a bile leak who required operative cholecystostomy and one patient who had excision of a punctured Meckel's diverticulum.

Percutaneous cholecystolithotomy is an alternative to cholecystectomy in selected patients. The success rate should increase, and complications decrease with greater experience and refinements of technique and equipment.

Symptomatology after gall stone clearance in patients receiving extracorporeal shock wave lithotripsy

A DARZI, A L LEAHY, T M FEELY, W A TANNER, AND F B V KEANE (Dept of Surgery, Meath and Adelaide Hospitals, Dublin) Extracorporeal shock wave lithotripsy (ESWL) combined with bile salt therapy can only be justified as a treatment of gall stones if patients are symptomatically improved after stone clearance. This study compared symptoms in patients treated by ESWL and bile salt therapy with a group of patients treated by cholecystectomy.

Thirty seven gall stone patients successfully treated by ESWL and bile salt therapy (group A), with clearance confirmed by ultrasound examination and oral cholecystography, were prospectively reviewed up to nine months (mean six months) after completion of therapy. Symptoms were compared with 86 patients reviewed six months to three years (mean 20 months) post cholecystectomy (group B). Pretreatment symptoms were similar in both groups, and there was no statistical difference in symptoms after treatment in either A or B. Complete relief of symptoms was reported by 70% of ESWL patients and 69% after cholecystectomy.

These preliminary results indicate that stone clearance after ESWL relieves pain in 80% of patients, which is similar to the results in patients treated by cholecystectomy.

Does the duodenal infusion of high nutrient loads inhibit human pancreatic exocrine function?

A H RAIMUNDO, J ROGERS, P H FIELDEN, AND D B A SILK (Dept of Gastroenterology and Nutrition, Central Middlesex Hospital, London) It has recently been shown that the infusion of high caloric loads (3-3 kcal/min) into the normal human jejunum inhibits exocrine pancreatic function. The present study was undertaken to determine whether this phenomenon occurs in response to high nutrient loads delivered by continuous intraduodenal enteral feeding.

Seven normal subjects (mean age 22 years, 21-25) were intubated with an 11-lumen orocaccal tube. Intestinal contents were aspirated at 30 minute intervals from the terminal ileum four hours before and four hours during continuous duodenal infusion (2-8 ml/min=4-2 kcal/min) of an energy (1-5 kcal/ml) and nitrogen (7-8 gN/l) dense polymeric enteral diet. Ileal trypsin concentration during diet infusion (mean (SEM) 222±1 (57-5) IU/l) was significantly (p<0.02) greater than basal (40-0 (7-7)) as were luminal concentrations of chymotrypsin (830±6 (227-7) IU/l v 343±3 (63-0), p<0.05) and lipase (8944±6 (2707-6) IU/l v 1315 (440-9) p<0.05).

These data show that the infusion of high loads of carbohydrate and nitrogen into the human duodenum stimulates rather than inhibits pancreatic exocrine function. Thus intestinal assimilation of high loads of nutrients administered during continuous intraduodenal enteral feeding is unlikely to be impaired as a consequence of inhibited pancreatic function.

Intraduodenal v oral test meals: avoiding marker/feeding separation

F H DRABLE, M F GRAHAN, L HINIC, P DEAN, N GARGEY, D I WINGATE, AND N S WILLIAMS (Surgical Unit, GI Science Unit, and Radioisotope Dept, The London Hospital Medical College and London Hospital, London) Since 1957, small bowel absorption measurement has depended on non-absorbable marker labelling of oral test meals, allowing compensation for meal dilution when measuring concentrations of fat, protein, and carbohydrate in gut aspirate. Intragastric fat/marker separation would render this method inaccurate. We have therefore compared the degree of fat/marker separation after oral, and after intraduodenal (ID) infusion of a standard liquid meal. Five normal volunteers (ages 20-22 years) swallowed an orojeunal tube and received two 250 ml Ensure test meals labelled with three non-absorbable markers, "^14C" and "^55S"TcSn, colloid, and phenol red. One meal was infused ID for 60 minutes and one swallowed mean (SEM) 192±5 (12-0) minutes later. Jejunal samples were aspirated continuously from two sites 40 cm apart.

Fat/marker ratios in jejunal samples aspirated within the first hour after oral Ensure were up to 6-5 times greater than the original meal ratio. In the same period, distal (aboral) fat concentration was greater than in proximal aspirates in 75% of samples with no corresponding rise in marker concentrations. Such marked intragastric and intra-small bowel fat/marker separation was not apparent in aspirate obtained during ID Ensure infusion.

Intraduodenal, not oral, liquid meals allow accurate measurement of small bowel absorption.

Differential D-xylene/3-O-methyl-D-glucose absorption in coeliac disease

S P L TRAVIS, I S MENZIES, AND B CREAMER (Rayne Institute and Department of Chemical Pathology, St Thomas's Hospital, London) Discrimination obtained by the 5 g D-xylene (Xyl) test in coeliac disease was
greatly improved by adding 3-O-methyl-D-glucose (3mGlc) and measuring plasma Xyl/3mGlc concentration ratios.

Nineteen fasting patients with untreated coeliac disease and 26 healthy controls drank Xyl 5 g, 3mGlc 2.5 g (+lactulose 5 g and L-rhamnose 1 g for permeability assessment) in 250 ml water (280 mOsmol/l). Blood was taken at 30 and 60 minutes and urine collected for five hours. Test sugars were estimated by quantitative thin layer chromatography.

Urinary Xyl in coeliacs and controls differed significantly (mean (SD) 18.7 (7.9) v 33.7 (5.7)% of oral dose, p<0.001) but five of the 19 coeliacs had a normal result (>22.3%, mean – 2 SD). Plasma Xyl concentrations were within normal limits (mean (2 SD) in 11 coeliacs at 30 minutes (0.68 (0.42) mmol/l) and in four at 60 minutes (0.85 (0.30)). Plasma 3mGlc showed no significant difference. Urinary Xyl/3mGlc ratios did not improve group separation but plasma Xyl/3mGlc completely separated patients from controls. Plasma Xyl/3mGlc ratios in coeliacs ranged from 0.44-0.85 (mean 0.59) at 30 minutes and 0.23-1.06 (mean 0.72) at 60 minutes compared with normal ranges (mean (2 SD)) of 0.91-1.67 and 1.11-1.71.

We conclude that estimating mediated intestinal absorption by plasma Xyl/3mGlc concentration ratios more effectively discriminates between untreated coeliac disease and controls than plasma or urine xylose alone.

Comparison of systemic and mucosal humoral immunity in coeliac disease

S O’Mahony, E Arranz, J R Barion, and A Ferguson (Gastro-Intestinal Unit, University of Edinburgh and Western General Hospital, Edinburgh) Previous studies of humoral immunity in coeliac disease have concentrated mainly on serum antibodies; the intestinal immune response has been relatively neglected. We measured immunoglobulin concentrations (IgA, IgM, and IgG) and antibodies to gliadin in serum, pure parotid saliva, and jejunal aspirate from 26 untreated coeliac patients, 22 treated patients, and 28 controls.

High concentrations of jejunal aspirate IgA, IgM, and IgG were found in the untreated group with normal concentrations in the treated group. Salivary and serum immunoglobulin concentrations were similar in the three groups.

Untreated coeliac patients had high values of antigliadin antibodies; these were predominantly in the IgA and IgG classes in serum and saliva, but in the IgA and IgG classes in jejunal aspirate. Whereas serum and salivary antibody concentrations were low in the treated group, intestinal antibody (particularly IgM antigliadin antibody) persisted, indicating a dissociation between systemic and intestinal immune response.

Saliva cannot be used in immune studies as a representative gastrointestinal secretion; salivary antibody concentrations were raised only in a minority of untreated patients and there was a poor correlation between antibody concentrations in saliva and jejunal aspirate.

Magnesium deficiency in Crohn’s disease: response to magnesium loading

J Walsh, W F Hawley, and B E Lane (Dept of Surgery, Jervis Street Hospital and Dept of Surgery, Beaumont Hospital, Dublin)

Hypomagnesaemia has been described in Crohn’s disease and may be exacerbated by surgery, sepsis, malnutrition, and parenteral nutrition, but preoperative magnesium assessment is rarely performed. It is associated with poor wound healing, psychiatric disturbance, paralytic ileus, and cardiac arrhythmias. This study aimed to determine the incidence of magnesium deficiency and response to magnesium loading in Crohn’s disease.

Serum and 24 hour urinary magnesium concentrations were estimated in 10 consecutive patients presenting for elective surgery and in 10 age and sex matched controls admitted for minor surgery. Crohn’s patients received a loading dose of 40 mmol magnesium sulphate in 1000 ml 5% dextrose and serum, and urine magnesium concentrations were estimated. The mean (SEM) magnesium concentration in Crohn’s patients was 0.75 mmol/l (0.02) compared with 0.91 mmol/l (0.07) in controls (p<0.05). Median 24 hour urinary magnesium level was 1.46 mmol/24 hours (all subnormal) compared with 3.47 mmol/24 hours in controls (p<0.01). After the loading dose serum magnesium rose to 1.04 (0.09) mmol/l (p<0.001), median urinary magnesium rose to 6.53 mmol/24 hours (p<0.001) and eight of 10 increased greater than 25% of the loading dose. Routine serum and urinary magnesium concentration estimation and magnesium sulphate administration is advised in all Crohn’s patients presenting for surgery.

Novel cell lineage in human intestinal mucosa induced by ulceration which secretes epidermal growth factor

N A Wright, C Pike, and G Elia (Royal Postgraduate Medical School and Imperial Cancer Research Fund, London) Epidermal growth factor/tuigastrogastric (EGF/URO) is a peptide of known growth promoting and cytoprotective function, produced by salivary and Brunners’ glands; its role in gastrointestinal homeostasis is obscure.

In abnormal conditions, when there is mucosal ulceration, our three dimensional studies show that new tubules grow out of the crypt base area, where stem cells are housed. These tubules then ramify in the lamina propria, and eventually grow upwards through the connective tissue core of the villus, and communicate with the surface epithelium via a stoma. The new tubules are lined by a distinctive cell, which secretes neutral mucin and is non-proliferative. These cells migrate along the tubules and onto the villus surface. Studies on their phenotype indicate that this cell lineage is unique among gastrointestinal cells, and is thus not a metaplasia. These cells also differentiate as they move onto the villi and secrete immunoreactive EGF/URO. We propose that in disease states, intestinal, and indeed all gastrointestinal stem cells can give rise to a unique new lineage capable of producing growth factors which aid mucosal regeneration; this mode of action of EGF/URO is likely to be an important new physiological intestinal mucosal defence mechanism. We also introduce the novel concept that abnormal conditions direct stem cell differentiation along singular pathways.

Geographic variation in intestinal permeability

A P Jenkins, I S Menzies, W S Nukaim, I Grellier, V I Mathan, and B Creamer (Depts of Gastroenterology and Chemical Pathology, St Thomas’s Hospital, London and Dept of Gastroenterology, Christian Medical College, Vellore, India) United Kingdom residents visiting tropical countries may experience an increase in intestinal permeability shortly after arriving abroad despite having no symptoms. To investigate geographic variation of intestinal permeability in asymptomatic indigenous subjects the urinary excretion ratio of ingested lactulose to rhamnose was measured.

Asymptomatic indigenous adults were recruited in the United Kingdom (n=58), Athens, Greece (n=32), Parma, Italy (n=18), Papua, New Guinea (n=17), Jakarta, Indonesia (n=25), Thailand (n=25), Vellore, South India (n=21) Gambia (n=8).
26), Botswana (n = 16), the Cameroons (n = 17), and Kingston, Jamaica (n = 14). Each subject ingested an iso-osmolar solution containing 1-0 g L-rhamnose and 5-0 g lactulose, after overnight fast. Five hour urine test sugars were measured by quantitative thin layer chromatography, the results expressed as per cent oral dose and the lactulose/rhamnose ratio derived.

The lactulose/rhamnose ratios (means (SEM)) in ascending order or magnitude were: United Kingdom 0-026 (0-001), Botswana 0-034 (0-003), Greece 0-037 (0-002), Italy 0-038 (0-004), South India 0-052 (0-008), Jamaica 0-054 (0-009), Thailand 0-055 (0-007), the Cameroons 0-064 (0-01), Indonesia 0-067 (0-007), Gambia 0-096 (0-019), and New Guinea 0-156 (0-024). The ratio from the United Kingdom group was significantly lower than the ratios from Botswana (p < 0.005) and each of the other countries (p < 0.001).

We conclude that intestinal permeability among asymptomatic indigenous adults varies geographically. This may reflect local gut microbiology, and perhaps differences in diet and ethnic origin.

Use of a model of human cholera to study hypotonic oral rehydration solutions

J B HUNT, S CARNABY, AND M J G FARRING (Dept of Gastroenterology, St Bartholomew’s Hospital, London) Currently available oral rehydration solutions (ORS) have been developed empirically and are usually hypertonic, which may inhibit water absorption. We have developed a model of secretory diarrhoea in man using highly purified cholera toxin (15 µg) introduced into a closed 30 cm segment of jejunum isolated between two occluding balloons. After two hours the balloons are deflated and one hour later a triple lumen perfusion is performed. We have used this model to compare water and sodium absorption from the most widely used ORS in the UK, UK-ORS (Na 35, Bic 18, Glu 200 mmol/l, Osm 310 mOsm/kg), a new HYPO-ORS (Na 60, Cit 10, Glu 90 mmol/l, Osm 240 mOsm/kg), and a plasma electrolyte solution (PES; Na 140, Bic 40, K 4, Ca 104 mmol/l, Osm 288 mOsm/kg). Secretion of water and sodium occurred during PES perfusion. HYPO-ORS produced greater water absorption than UK-ORS (5-9 (2-4) v 2-7 (1-7) ml/cm/h; n = five; p < 0.05). Sodium secretion occurred with UK-ORS (280±1 (167-6) µmol/cm/h; n = five) but absorption with HYPO-ORS (122-6 (264-8) µmol/cm/h; n = five; NS).

HYPO-ORS promoted greater water absorption than UK-ORS in this secretory model in man. HYPO-ORS may offer clinical advantages with respect to water absorption during acute diarrhoea in children and thus warrants clinical trial.

COLORECTAL III

Is the survival rate in colorectal cancer improving?

P J CULLEN, V KOMOROSZ, M SARNER, AND P B BOULOS (Depts of Surgery and Gastroenterology, University College London, The Rayne Institute, London) It is generally accepted that over recent decades there has been little improvement in survival in colorectal cancer (CRC). We have examined the course of the disease in patients seen over the last decade and compared it with an earlier period before the provision of a specialised service. The case notes of all patients presenting with CRC between 1970 and 1989 were reviewed. Group I consisted of 493 patients treated between 1970 and 1979, and group II, 360 treated between 1980 and 1989. The mean age was 66-6 (11-6) v 67-6 (11-8) years, p = 0.5. No differences were detected in tumour distribution. Colorectal cancer was diagnosed at a more favourable stage in group II when compared with group I (Dukes A: 11-4% v 6-5%; p < 0.01, B: 51-7% v 44-6% p < 0.05, C: 36-9% v 48-9% p < 0.01); there was a significant increase in the proportion of moderately well differentiated tumours (66-4% v 58-8%; p < 0.05), and a decrease in the number of advanced carcinomas (modified Dukes D) (15-8% v 23-9% p < 0.05). The primary tumour was resected in 88-2% of patients in group I and 94-7% of those in group II, p < 0.001. The postoperative mortality decreased over the two decades from 11-6% to 5-8% p < 0.01. Cumulative survival probability was significantly better in group II (p < 0.001) with a median survival of 76 months compared to 31 months in group I.

Our results show considerable improvement in the outlook of patients with CRC over the last decade due to the provision of a specialised service with an interest in CRC.

Perioperative blood transfusion has no influence on recurrence in colorectal cancer

N C ARMIDGE, K C BALLANTINE, AND J D HARDCASTLE (Dept of Surgery, University Hospital, Nottingham) There is controversy as to whether perioperative blood transfusion in patients with colorectal cancer has an adverse effect on immune responses and therefore on survival. Most reports, however, have been retrospective. We investigated prospectively the influence of perioperative blood transfusion on tumour recurrence in patients with colorectal cancer.

We studied 299 unslected patients who underwent resection for colorectal cancer—median follow up 35 months (12-72 months) and were followed in a specifically constituted clinic.

Overall, 147 (49%) patients were transfused. There was no relation between transfusion and stage or grade. Patients with left sided colonic tumours — 23 of 86 (30%), were transfused less often than those with right sided or rectal tumours — 124 of 223 (55%) (χ2 = 13-6, p = 0.0002), whereas 53 of 83 (64%) patients with fixed tumours were transfused compared with 93 of 213 (46%) with mobile tumours (χ2 = 8-9, p = 0.003). Considering patients undergoing curative surgery 33 of 100 who were transfused and 38 of 118 (32%) who were not, have developed recurrence. Transfusion had no influence on recurrence when patients were subgrouped by stage or tumour site.

At this time of follow up perioperative blood transfusion does not seem to influence recurrence and other factors are responsible.

Familial juvenile polyposis coli and colorectal cancer

D S O’RORHAIN, E W MCDERMOTT, A F CULLEN, AND J J MURPHY (St Vincent’s Hospital, Dublin) Accumulating evidence suggests an association between juvenile polyposis coli and colorectal cancer. We present a juvenile polyposis coli family which supports the malignant potential of juvenile polyposis and which suggests a mechanism through which this neoplastic change may occur.

A 40 year old mother had a colectomy for polyposis coli. The resected colon contained predominantly juvenile polyps but also tubular adenomas, some of the latter containing dysplastic areas. The transverse colon contained a 5 cm villous adenoma with areas of severe epithelial dysplasia but no invasive malignancy.

Her seven year old son presented subsequently with rectal bleeding and juvenile polyposis coli was diagnosed. Because of his family history, and the number of polyps...
Bromodeoxyuridine labelling – a novel biomarker of colonic cancer risk

R G Wilson, C C Bird, and A N Smith (University Dept of Surgery, Western General Hospital, Dept of Pathology, University of Edinburgh Medical School, Edinburgh) Immunohistochemical detection of bromodeoxyuridine (BRDU) incorporation by proliferating cells was studied in the large bowel mucosa of adenoma subjects. Biopsy specimens were labelled in vitro from 10 adenomas and 10 age and sex matched controls. The relative position and percentage of labelled cells within 20 axially sectioned crypts were recorded for each biopsy. Differences in the colonic crypt proliferative compartments were compared by generation of cumulative labelled cell distributions (CLDs). The mean labelling index was increased at all sites examined in polyp subjects (Student’s t test p<0.001). Comparison of CLDs at each site showed a significant expansion of the proliferative compartment towards the luminal surface in polyp subjects (Kolmogorov-Smirnov two sample test p<0.01).

A further prospective study of sigmoid biopsy specimens from 20 control and 20 polyp patients was performed. Comparison of these subjects’ individual CLDs to the original sample groups yielded a sensitivity of 0.8 (16 of 20), a specificity of 0.85 (17 of 20), with a positive predictive value of 0.84.

We conclude that cell proliferation is abnormal throughout the large bowel in the presence of adenomas. BRDU labelling provides a useful biomarker for application in human studies of colon cancer prevention.

Truncal vagotomy alters duodenal bile acid profile

F J Mullan, G R Campbell, and S D McKenny (Dept of Surgery, Queen’s University, Belfast and The Ulster Hospital, Belfast) Bile acids may promote colorectal carcinogenesis. The increased risk of colorectal neoplasia after truncal vagotomy may be related to abnormalities in the bile acid pool.

Duodenal bile acids of 13 truncal vagotomy patients (10 male, three female; mean age 63-6 years) and 13 controls, matched for sex and as closely as possible for age, were compared. All had normal gall bladders. Duodenal bile was collected at endoscopy and analysed by high performance liquid chromatography. Conjugates of cholic (CA), chenodeoxycholic (CDCA), deoxycholic (DCA), and lithocholic (LCA) acid were detected and expressed as % total bile acids present. The mean percentage of CA, CDCA, DCA, and LCA in the bile of vagotomised patients was 32.9, 44.3, 21.6, and 1.1% respectively compared with 43.2, 36.3, 19.6, and 0.9% respectively in control patients. The decrease in the proportion of CA (p<0.009) and the increase in CDCA (p=0.05) were both significant (Wilcoxon’s sign rank test). This abnormality of duodenal bile is similar to that previously reported in patients with colorectal neoplasia.

We conclude that abnormalities of duodenal bile acids are present after truncal vagotomy and may contribute to the development of colorectal neoplasia.

Neoplasia of the human colon is associated with changes of copper/zinc containing proteins

P J Mulder, H W Verspaget, A F Janssens, P A F De Bruin, G Grijzenhout, and C H W Lammers (Dept Gastroenterology and Hepatology, University Hospital, Leiden, The Netherlands) Copper (Cu)/zinc (Zn) containing proteins have recently become of interest with regard to their relation to malignancy. Cu/Zn-superoxide dismutase (SOD) has been found to be increased in tumours whereas metallothionein (MT), containing Zn and some Cu, has been shown to be of importance in the response to chemotherapy. In the present study we evaluated the SOD and MT content in normal mucosa and colorectal carcinomas obtained from resection specimens (n=19), and in adenomatous polyps (n=47) obtained by endoscopic polypectomy. Tissue samples were partly processed for routine histology and partly homogenised for SOD determination by ELISA and MT determination by RIA. The results were expressed as μg SOD or MT/mg protein and evaluated by the Wilcoxon’s rank-sum test.

The SOD content of adenomatous polyps (2.72 (0.0)3) and carcinomas (2.93 (0.1)) was significantly higher (p<0.01) than that of normal mucosa (2.13 (0.10)). Within the adenomatous polyps, the SOD content increased with the grade of epithelial cell dysplasia (mild: 2.39 (0.21), moderate: 2.58 (0.19), severe: 2.96 (0.25), and with invasive growth: 3.01 (0.41). The MT content was significantly decreased (p<0.001) both in adenomatous polyps (0.28 (0.03)) and carcinomas (0.25 (0.01)) compared with that of normal mucosa (0.44 (0.03)). No relation was found between the grade of epithelial cell dysplasia and the MT content in the polyps.

We conclude that neoplasia in the colorectum is accompanied by an increase in Cu/Zn SOD and a decrease in Cu/Zn MT. These findings support the association between changes in Cu/Zn proteins and malignancy. Because MT may function as a Cu/Zn donor for other intracellular metalloproteins the decrease in MT content in colorectal neoplasia could partly be due to the increase in SOD content.

Vitamins A, C, and E and lactulose in the prevention of recurrence of adenomatous polyps: preliminary results of a controlled study

M Ponzo de Leon, I Roncucci, P Di Donato, M Zini, C Paganini, A Antonioli, A Ferrari, B Paris, A Svanoni, and M Girola (Istituto di Patologia Medica e Cattedra di Gastroenterologia, Universita’ di Modena, Divisione di Medicina III, Ospedali Riuniti, Bergamo, Italy) After endoscopic removal, adenomatous polyps – the natural precursors of colorectal cancer – tend to recur in 30–40% of the patients. We aimed therefore to evaluate whether long term oral administration of vitamins (because of their antioxidant effect) or lactulose (which lowers intestinal pH, thus limiting the production of carcinogen secondary bile acids) reduces the recurrence of colorectal polyps.

After endoscopic excision of polyps, 219 patients were randomised into three groups. Seventy two were given vitamin A, C, and E (30000 U, 1 g, and 70 mg/day respectively) 69 were given 20–40 g of lactulose, and 78 received no therapy. Endoscopies were undertaken at six, 12–18, and 24 months. Among the 114 patients followed for at least 12–18 months, adenomatous polyps recurring in three of 39 (7.6%) treated with vitamins, in 10 of 36...
(27.7%) who received lactulose, and in 16 of 39 (41.0%) untreated. These differences were statistically significant ($\chi^2 = 9.8, p<0.01$) by life tables and log rank test, basically because of the effect of vitamins.

These preliminary results suggest that either vitamins or lactulose may lower the recurrence rate of colorectal polyps, though the effect is more marked for vitamins. These agents, therefore, should be further investigated in order to achieve effective prevention of large bowel cancer.

**PLenary SESSION**

**Use of late N-acetyl cysteine in severe paracetamol overdose**

R I KEAYS, C Gove, A FORBES, G J M ALEXANDER, AND R WILLIAMS (Liver Unit, King’s College Hospital and School of Medicine and Dentistry, London) The hepatoxicity of paracetamol is due to the formation of a highly potent oxidising agent which has overwhelmed the normal mechanisms of disposal Normally glutathione (GSH) is oxidised to glutathione disulphide (GSSG) with the formation of covalent thiol adducts, but if GSH stores are depleted, liver damage can develop. Administration of N-acetyl cysteine (NAC) after the first 16 hours post-ingestion was felt not to be beneficial in preventing this, although its free radical scavenging abilities theoretically may be useful in limiting oxidative damage. Twenty nine patients (aged 16-56 years, male=10, female=19) presenting with FHF >36 hours after paracetamol overdose and without prior treatment with NAC were randomised to treatment or control groups. Treatment comprised NAC 150 mg/kg bolus followed by 50 mg/kg over four hours and then 100 mg/kg/16 hours until resolution of coma or death. At entry both groups were similar and there was no significant difference between the groups in terms of peak prothrombin time (PT), maximum grade of coma, or incidence of cerebral oedema, renal failure, and acidosis. Of the 14 patients in the NAC group, nine survived as opposed to three of 15 in the controls ($\chi^2$Yates modification $p<0.05$). In those who survived the time taken for the peak PT to fall to within 20 seconds prolonged was similar in each group (range three to six days).

NAC treatment for paracetamol induced FHF more than 36 hours after ingestion was associated with a significantly improved survival.

**O'-Methylguanine methyltransferase in the human stomach**

W J CRISP, M LUNN, S A RAIMIES, C W VENABLES, A L HARRIS, AND I D A JOHNSTON (Dept of Surgery and the Cancer Research Unit, The Medical School, University of Newcastle upon Tyne) N-nitroso compounds damage DNA in vitro. The most important mutagenic adduct is alklylation of the O' atom of guanine (O'-methylguanine). On DNA replication this causes mispairing with thymidine. O'-methylguanine methyltransferase (O'-MG MT) is a specific suicide protein that removes the methyl group and repairs the DNA in an error free manner. Activity of this protein in the gastric mucosa may reflect exposure to carcinogens acting via O'-methylguanine.

The aim of this study was to assess O'-MG MT as an objective measure of malignant change in the stomach. O'-MG MT activity was assayed in biopsy specimens taken with endoscopic forceps from:

1. Gastric resections for adenocarcinoma (a) from the tumour itself, and (b) mucosa at 5 mm from the microscopic margin of the tumour.
2. Mucosa from patients with non-ulcer dyspepsia or an untreated duodenal ulcer.

There was a highly significant difference in O'-MG MT activity between tumour, mucosa surrounding a tumour, and control mucosa. The increased activity may be induced in response to alkylating carcinogens and may provide an objective marker of malignant and premalignant change.

**Role of epidermal growth factor in regulation of gastric secretion**

A GARNER, H GREGORY, S E HAMPSHIRE, A M STANIER, AND I R WILLSHIRE (Bioscience Dept, ICI Pharmaceuticals, Macclesfield, Cheshire) Epidermal growth factor (EGF) is a potent antagonist of acid secretion after parenteral injection. In the anaesthetised rat, human EGF (urogastrone) inhibited dimapir-stimulated acid output with an IC-50 of 0.5 µg/kg iv. We have developed a high titre, affinity purified polyclonal antiserum against human EGF which cross reacts with rodent EGF but not with human TGFα. Complete neutralisation of the antisecretory activity of EGF (5 µg/kg iv) occurred when 150 µl of antiserum was injected into rats from four days up to one minute before EGF. However, when given as little as 1 minute after EGF, the full antisecretory response was observed indicating very rapid transduction of the signal leading to inhibition of H+ transport. Antiserum alone had no effect on basal secretion in the rat but increased dimapir-stimulated acid output by 30% suggesting that circulating EGF exerts inhibitory tone on the actively secreting parietal cell.

Paradoxically, EGF is secreted in substantial amounts into the lumen of the gut. although it is inactive orally. Thus luminal instillation of 100 µg/kg EGF in saline into segments of duodenum, jejunum, or ileum did not influence acid secretion. However, permeabilisation of the epithelial barrier by administration of EGF in 1 M NaCl resulted in a profound antisecretory response. These data show that bioavailability of the peptide is increased dramatically after superficial damage suggesting that luminal EGF exerts a ‘housekeeper’ function in respect of mucosal protection and repair.

**DP alleles do not independently confer susceptibility to coeliac disease**

W ROSENBERG, P WORDSWORTH, J BELL, AND D P JEWELL (Dept of Gastroenterology and Nuffield Dept of Medicine, John Radcliffe Hospital, Oxford) Coeliac disease (CD) has been shown to be strongly associated with (HLA) B8 and DQW2 with DR3, 7, or 5. Restriction fragment length polymorphism (RFLP) studies suggest that HLA-DP genes may also be associated with CD. We have cloned and sequenced HLA-DPB genes from one CD patient with and two without the B8 DR3 DQW2 haplotype associated with CD. No sequences were common to all three patients. Sequence specific oligonucleotide (SSO) probes were subsequently used for DP typing. DNA was amplified by polymerase chain reaction (PCR) from 36 patients with CD. 48 DR3 positive ethically matched controls and 62 randomly matched controls. HLA DPB1 occurred in 50% of CD patients but in only 5% random controls. However, when compared with DR3 positive individuals, no significant difference in the frequency of DPB1 was found.

This suggests that the association of DP alleles with CD is due to the linkage disequilibrium observed between HLA DPB1 and the B8 DR3 DQW2 extended haplotype. Furthermore, it suggests that the mutation susceptibility gene for CD located in chromosome 6 lies telomeric of the DP locus.
Prospective randomised trial of by pass surgery v endoscopic stenting in patients with malignant obstructive jaundice

A C SMITH, J F DOWSETT, A R W HATFIELD, R C RUSSELL, S J WILLIAMS, C C AINLEY, P R COTTON, A G SPIER, J HOUGHTON, T LENNON, and K MACRAE (Dep's of Gastroenterology and Surgery, The Middlesex Hospital and The CRC Clinical Trials Centre, Kings College School of Medicine and Dentistry, London) Over a 3-5 year period, 170 patients with obstructive jaundice (bilirubin >100 µmol/l) caused by primary unresectable bile duct malignancy, and with no contraindications to surgery, were prospectively randomised to surgical bypass or endoscopic stent insertion. All had normal duodenums and no previous endoscopic or surgical intervention. There were no significant differences in age, sex, or risk factors between groups. Eighty five patients underwent a by pass and 85 were stented. Successful drainage was obtained after surgery in 81 of 85 (95%) and after stenting in 81 of 85 (95%). In 20 patients stenting was achieved using a combined percutaneous/endoscopic technique. Major complications occurred in 29 of 85 patients after surgery and 19 of 85 after stenting, and minor complications in 19 of 85 and 13 of 85 patients respectively. The 30 day mortality was 18.8% (16 of 85) after surgery and 7% (16 of 85) after stenting (p<0.05). Direct procedure related mortality was 10% (nine of 85) after surgery and 1% (one of 85) after stenting (p<0.01). A total of 54 surgical and 55 stenting patients have died; the mean survival for surgery was 19.5 weeks and 24 weeks for stenting. There is no statistical difference in the life table analysis for survival. The incidence of late duodenal obstruction was 2% (two of 85) after surgery, one needing further surgery, and 16.4% (14 of 85) after stenting (p<0.02), five needing gastric bypass surgery. Recurrent jaundice occurred in three of 85 patients after surgery (3.5%) and in 17 of 85 after stenting (20%) (p<0.001), needing stent replacement.

We conclude that endoscopic prosthesis insertion and surgical bypass are equally successful in the relief of malignant low biliary obstruction. In the surgical group fewer patients subsequently developed recurrent jaundice or gastric outlet obstruction but endoscopic stenting results in a significantly reduced procedure related mortality, 30 day mortality, and major morbidity. However, the longer term survival between the two groups is similar and readmission was rarely needed in the surgical group but was necessary in the stented group for reasons of gastric outlet obstruction and stent blockage.

Role of the colon in maintaining sodium homeostasis in young children

Y FINKEL, H R JENKINS, and I W BOOTH (Institute of Child Health, University of Birmingham, The Children’s Hospital, Birmingham, and Cardiff Royal Infirmary, Cardiff) There are few data in children on the homeostatic responses of the colon to Na depletion. We have studied eight ileostomy patients (median age 160 days, range 45-420, median weight 3.57 kg, range 3.115), before and after the ileostomy closure, using non-equilibrium rectal dialysis and 24 hour Na balances. Rectal Na absorption and K secretion (nmol/min/cm²) were significantly higher in the children with a negative or low positive Na balance (n=seven, median Na balance +0.05 mmol/kg/24 hour; median Na absorption 238; median K secretion 89) compared with those with a large positive sodium balance (n=six, median Na balance +2.42 mmol/kg/24 hour, p<0.05; median Na absorption 138, p<0.05; median K secretion 42, p<0.05). While median rectal Na absorption and K secretion before and after closure of the ileostomy were similar and not different from controls, Cl absorption (nmol/min/cm²) was significantly lower before (median 139, range 65-231) than after (median 175, range 134-259, p<0.05).

These data indicate that rectal, and presumably colonic, electrolyte transport is enhanced in children with a negative or low Na balance, and that Cl but not Na absorption is depressed by the temporary diversion of ileal effluent.

Value of paediatric duodenoscopes for endoscopic retrograde cholangiopancreatography in children

M I WILKINSON (Gastroenterology Unit, United Medical and Dental Schools, Guy’s Campus, London) Investigation of pancreatic and biliary diseases in infants under two years has been facilitated by the advent of prototype paediatric duodenoscopes (Olympus PJJ 7-5 and XPJJ 8-0). The present report details experience in their first 19 uses in 18 children aged 2-86 (median 11) months, including nine with neonatal or early postnatal conjugated hyperbilirubinaemia (CH) (aged 8-56, median 18 weeks) and 10 with other biliary or pancreatic conditions (aged 6-42 months). The procedure was technically successful in 18 cases, without complications. In the nine CH cases, extrahepatic biliary atresia was disproved in five
and strongly suggested in three (subsequently confirmed at laparotomy) by ERCP. Other diagnoses were: paucity of intrahepatic bile ducts (two), common hepatic duct block (one), and sclerosing cholangitis (one). In two who subsequently improved, the cause of cholestasis was not delineated. Of the non-CH patients, four with suspected choledochal cysts were shown to have: type 3 cysts (one), no abnormality (two), reduplication cyst communicating with biliary tree and pancreas (one). A child with recurrent pancreatitis also had a reduplication cyst of the pancreatic head on two ERCPs. In three, gall stones (gall bladder, Hartmann’s pouch, and common bilipancreatic channel) were shown. In a child (68 months) with suspected choledocholithiasis a complete biliary blockage due to surgical trauma was demonstrated.

Endoscopic retrograde cholangiopancreatography in infants is safe and has a high diagnostic yield in selected cases. It is a useful adjunct to diagnosis in difficult cases of neonatal CH.

Hyperventilation provokes pain and alters oesophageal motility in patients with angina-like chest pain

R M Valori, E Cole, M Lemon, J A Dunn, and R Cockell (Selly Oak Hospital and Queen Elizabeth Hospital, Birmingham) Hyperventilation and disorders of oesophageal motility have been linked with angina-like chest pain (ACP). This study examined the effects of hyperventilation on oesophageal motility in patients with ACP but without evidence of coronary artery disease.

Fifteen patients with ACP underwent a manometric study 3, 8 and 13 cm above the lower sphincter before, during, and after enforced hyperventilation to an end-tidal pCO$_2$ of 3 kPa. Means were compared using analysis of variance. The mean propagation velocity of 10 wet swirls increased from 3.7 to 4.2 cm/sec during hyperventilation (p<0.001). The mean amplitude of contraction increased from 58.3 to 65.7 cm H$_2$O after hyperventilation (p<0.04). This increase was associated with a fall in heart rate (p<0.01). Eight patients (53%) experienced their usual chest pain during or after hyperventilation, or both. In this group more spontaneous events occurred (28 v 10) but hyperventilation did not induce spontaneous activity and pain was not closely related to manometric events.

In conclusion, patients with ACP should be discouraged from hyperventilating during oesophageal manometry as spuriously high estimations of amplitude and propagation velocity can occur. While patients with hyperventilation-induced ACP have more frequent spontaneous activity, the poor correlation between events and pain suggests that hyperventilation provokes chest pain by another mechanism.

What are the benefits of an oesophageal laboratory?

W J Owen, M Mccullagh, and A Anggiansah (Dept of Surgery, Guy’s Hospital, London) An oesophageal laboratory is demanding of expertise and expense and its role should therefore be assessed.

The records of 481 patients referred to an oesophageal laboratory for investigation of chest pain or dysphagia, or both, were analysed in order to compare the results of the standard oesophageal investigations of endoscopy and barium swallow examination on the one hand with investigations in a specialised oesophageal laboratory on the other.

In the laboratory, patients underwent 24 hour ambulatory pH monitoring (Synctics) and oesophageal manometry (Gaeltec), including intravenous carbon dioxide provocation. The final laboratory diagnoses are as follows showing the number in each group in square brackets, compared with the number correctly diagnosed on the basis of barium swallow and endoscopy. Achalasia [27] (19%); diffuse spasm [48] (26%); scleroderma [11] (7%); and reflux disease [25] (60%).

Thus, of 481 patients referred, 138 were correctly diagnosed only as a result of using pH monitoring and manometry, and would have been misdiagnosed on the basis of barium swallow and endoscopy alone.

The laboratory results in an improved diagnostic yield of 29%.

High diagnostic yield of a dyspepsia clinic

G M Sobala and A F R Axon (Gastroenterology Unit, The General Infirmary, Leeds) In 26 months of a dyspepsia clinic (DC) offering GPs rapid access to endoscopy services, 1119 patients were endoscoped, usually within two to three weeks of referral. Pretreatment with H$_2$ antagonists was discouraged. Some 21-1% of DC patients had peptic ulcers, compared with 14.5% of 5619 hospital referred patients over the same time (p<0.0001). Thus in the DC duodenal ulcers were picked up at twice the rate while gastric ulcers were picked up at the same rate. This was probably due to the shorter time between referral and endoscopy in the DC and to the lack of pretreatment with H$_2$ antagonists. A total of 17 DC patients, all over age 45 years, had malignant neoplasms and seven of the 11 gastric cancers underwent potentially curative surgical resection. A total of 73 GPs replied to a questionnaire about the DC: 26-7% felt that their prescribing of H$_2$ antagonists had declined as a result of the DC, whilst 13-3% felt that it had increased. Fifty per cent now had to spend less time with dyspeptic patients while only 6-3% spent more. Some 92-1% felt that even a normal endoscopy made management easier.

We conclude that a DC has a high diagnostic yield and improves the ability of GPs to manage dyspepsia.

Design and testing of a new single stitch endoscopic sewing machine

P Swain, G Brown, N Van Someren, D Wimgate, and T Mills (Dept of Medical Physics, University College Hospital and Academic Dept of Gastroenterology, The London Hospital, London) We designed and tested a small diameter sewing machine for use with flexible endoscopes which has a novel mechanism designed to deliver strong single transmural nylon stitches remotely to gastrointestinal (GI) tissue. It works as follows. Tissue is sucked into cavity in machine’s body to form a double layer. A slotted hollow needle pierces this double layer. A plunging forces a nylon suture through hollow needle. The preformed T shaped distal part of the suture, flattened as it passes through the needle, opens up after being forced through tissue so that it cannot return. The needle is withdrawn, releasing the proximal part of the formed stitch through a slot. A simple pull and release action is transmitted through a wire wound cable. This sewing machine is front loaded with the control cable passing through the biopsy channel of a conventional endoscope, or manipulated by a paediatric endoscope parallel to the control cable. This machine was tested in postmortem human oesophagus (15 expts), stomach (50), jejunum (15), colon (15). The nylon has an 8 lb breaking strain. Sutures deep to muscularis propria require 3-4 lb force to pull them out; sutures deep only to muscularis mucosa require 0-75-1 lb. This device was used to attach radiotracery capsules, drug impregnated materials and feeding tubes to GI tissue at endoscopy. Design has...
allowed a reduction in outer diameter to 11 mm, the size of standard endoscopes. This machine simplifies placing stitches in GI tissue at flexible endoscopy.

**Controlled trial of polymeric elemental diet in the treatment of active Crohn’s disease**

M H Giafar, G North, and C D Holdsworth (Gastroenterology Unit, Royal Hallamshire Hospital, Sheffield) Amioco acid based elemental diets have been used in the management of patients with active Crohn’s disease with favourable results, but it remains controversial if the absence of intact protein is essential to their therapeutic effects. Twenty eight patients with active Crohn’s disease (mean Crohn’s disease activity index (CDAI) was 295), were randomised to receive either an amino acid based enteral feed (Vivonex-Norwich Eaton) n = 14, or a polymeric diet (Fortison – Cow & Gate) n = 14. All patients were initially assessed at 10 days and treatment was considered to have failed if symptoms persisted. Complications developed, and the CDAI remained $\geq 200$. Fortisone were offered Vivonex treatment but Vivonex failures were withdrawn from the study and treated with steroids or surgery. Of the Vivonex group, 11 patients entered clinical remission at 10 days (79%) compared with only five patients in the Fortison group (35%), p $\leq 0.02$. Responders to both treatments remained well on day 28. Vivonex resulted overall in a significant reduction of the CDAI (294 to 137, p $\leq 0.006$). In contrast, there was no significant change in the CDAI (297 to 217, p $\leq 0.5$) in the Fortison group. Five of the Fortison failures were treated with Vivonex of whom two achieved clinical remission; the remaining four were treated with surgery (two) and steroids (two). Three patients failed to respond to Vivonex; all responded subsequently to steroids. We conclude that an amino acid based elemental diet is more effective than a polymeric diet in the treatment of active Crohn’s disease.

**Pathogenesis of Crohn’s disease: multifocal gastrointestinal infarction**

A Wakefield, A Sawyer, A P Dhillon, A A M Lewis, and R E Pounder (Academic Dept of Medicine and Histopathology and Dept of Surgery, Royal Free Hospital School of Medicine, London) In a prospective study, specimens of resected small and large intestine from a series of 15 patients with Crohn’s disease have been prepared using combinations of: (1) heparin-saline perfusion and resin casting of the mesenteric vascular supply, followed by tissue clearance. (2) glutaraldehyde perfusion-fixation, resin casting and tissue clearance. Specimens were examined by microscopy, by conventional histopathology, and by scanning- and transmission-electron microscopy.

These examinations indicate a pathogenic sequence of events: vascular injury, focal arteritis, fibrin deposition, and arterial occlusion at a discrete level of the wall of the intestine, followed by tissue infarction or neovascularisation. These events are patchy in Crohn’s disease, and they do not occur in normal bowel.

We conclude that the results of these observations indicate that Crohn’s disease is mediated by multifocal gastrointestinal infarction, a pathogenetic process that is compatible with most clinical features of the disease.

**Post-cimetidine surveillance for up to 10 years: declining trends of carcinoma of the stomach and oesophagus**

D G Colin-Jones, M J S Langman, D H Lawson, M P Vessey, R Logan, and K Patterson (Queen Alexandra Hospital, Portsmouth; Birmingham; Oxford; Stratford; Nottingham) We have been carrying out a post-marketing surveillance study since 1978 on 9282 patients who received cimetidine at that time. Records have been flagged at the NHS central registries at Southport and Edinburgh so that we are notified of any patient who dies or is registered as having cancer. Data are complete for a minimum of seven years and a maximum of 10.

Altogether 141 cases of oesophageal or gastric cancer have been notified, of which 51 have been reported previously. A total of 111 patients had received cimetidine before the diagnosis of cancer; 71 had adenocarcinoma of the body/antrum, 27 had tumours of the cardia (22 adenocarcinoma, five unknown histology), and 13 had squamous carcinoma of the oesophagus. There were six early gastric cancers. The observed/expected ratios fell during the period of observation. O/E gastric cancer, 454/2 (year one), 83/4 (year four), 4/3/4 (year eight); for oesophageal cancer the corresponding ratios were 71/3, 21/4, and 6/1/5. No correlation could be found between cimetidine consumption and the subsequent development of a cancer.

There continues to be a slow but steady decline in the incidence of gastric cancer in the UK, which has not altered since the introduction of cimetidine. Furthermore, over the period of observation we have found no causal link between taking cimetidine and gastric cancer.

**Malevolent gall**

R H Diamond, M C J Barker, P Quirk, M D Dixon, and D Johnson (University Dept of Surgery and Pathology, and Dept of Nuclear Medicine, The General Infirmary, Leeds) Enterogastric reflux (EGR) has consistently been implicated in the pathogenesis of gastric cancer after ulcer surgery. We have studied the relation between the quantity of EGR and the development of gastric cancer in rats. EGR was measured using Tc-EHIDA, which is excreted in bile after intravenous injection. The ratio of gastric to total intestinal radioactivity after removal of stomach and small bowel is a measure of EGR. We have expressed this ratio as a percentage—the gastroenteric index (GEI).

Groups of 20 Wistar rats underwent gastrotomy (GAST), highly selective vagotomy (HSV), truncal vagotomy and pyloroplasty (TV + P) or truncal vagotomy and gastrojejunostomy (TV + GJ). They were fed the carcinogen MNNG (75 mg/l) in their drinking water for 14 weeks and killed 40 weeks after operation, with measurement of EGR.

The median GEI of each group after GAST (1.04), HSV (1.93), TV + P (2.80), and TV + GJ (10.30) correlated with the incidence of gastric cancer in each group which was 0%, 6%, 20%, and 38% respectively (r = 1, p < 0.05). The median GEI of rats with and without cancer from all groups was 7.71 and 2.09 (p < 0.01). When the GEI was less than 1 no cancers were found: when 2-5 the incidence was 11%, when 6-10 it was 40%, when 11-20 it was 50%, and when 21-40 it was 60%.

These results suggest the quantity of EGR is an independent risk factor in the development of gastric cancers, irrespective of the type of operation.

**Polyomavirus and primary sclerosing cholangitis—an aetiological link?**

J A Snook, W Mhale, J Kuritz, S D Gardner, J Clewley, D P Jewell, K Fleming, and R W G Chapman (Depts of Gastroenterology and
Histopathology, John Radcliffe Hospital, Oxford) The actiology of primary sclerosing cholangitis (PSC) is unknown. A latent viral infection with intermittent reactivation could account for the typically fluctuating course of PSC, the development of the condition in immunodeficiency states, and the increased risk of cholangiocarcinoma. Human polyomaviruses are potentially oncogenic, and enter a latent phase after primary infection. Reactivation has associated with a sclerosing cholangitis (PSC).

A raised antibody titre to polyomavirus, suggestive of recent reactivation, was found in 3% of 30 patients with inflammatory bowel disease, 3% of 28 patients with chronic ‘autoimmune’ liver disease, and 29% of 28 patients with PSC. The difference could not be accounted for by immunosuppressant exposure. A raised titre was present in seven of 13 (54%) of PSC patients with a serum AST concentration of over 100 IU/l. The polymerase chain reaction was employed to look for viral sequences in liver. Preliminary evidence of polyomavirus was found in five of nine PSC livers and three of seven disease controls. It is possible that PSC may result from hepatobiliary reactivation of latent polyomavirus infection in predisposed individuals.

Structure and evolutionary origin of the gene encoding a human serum mannose-binding protein

J A SUMMERFIELD, M E TAYLOR, P M BRICKELL, AND R K CRAIG (Dept of Medicine, St Mary’s Hospital Medical School, London and The Medical Molecular Biology Unit, University College and Middlesex School of Medicine, London) We have shown that human serum contains two calcium dependent carbohydrate specific binding proteins which have a high affinity for mannose terminated glycoproteins. The major human serum mannose binding protein (MBP1) is secreted by hepatocytes. We now report that the NH2-terminal sequence of MBP1 is identical to the amino acid sequence predicted from a cDNA clone of a human liver MBP mRNA. An oligonucleotide corresponding to part of the sequence of this cDNA clone was used to isolate a cosmid genomic clone containing the gene encoding this protein. The intron/exon structure of the gene was found to closely resemble that of the gene encoding a rat liver MBP (MBP A). The MBP molecule comprises a signal peptide, a cysteine rich domain, a collagen-like domain, a ‘neck’ region and a carbohydrate binding domain. The carbohydrate binding domain has marked homology with other carbohydrate binding proteins. Each domain is encoded by a separate exon. This genomic organisation lends support to the hypothesis that the gene arose during evolution by a process of exon shuffling. Consensus sequences, which may be involved in controlling the expression of human serum MBP, have been identified in the promoter region of the gene. These include a heat shock promoter, three glucocorticoid responsive elements, and a sequence homologous to that found in the promoter region of the serum amyloid A gene (SAA9). The consensus sequences are consistent with the hypothesis that this mammalian serum lectin is regulated as an acute phase protein synthesised by the liver.

Randomised controlled trial on the treatment of multiple colorectal liver metastases

J HUNI, A FLOWERDEW, S BIRCH, M MULEE, AND TAYLOR (University Surgical Unit, Dept of Radiology and Medical Statistics, Southampton General Hospital, Southampton) The treatment of patients with multiple colorectal liver metastases is highly controversial. Long term hepatic arterial infusion with FUDR has recently been recommended, but its benefit has not been proved and side effects are considerable. We have performed the first prospective randomised trial comparing no treatment with either hepatic arterial infusion of 5FU and starch degradable microspheres (HA1) or hepatic arterial embolisation (HAE). Of 81 patients referred for consideration 60 were eligible for randomisation. Mean age, percent hepatic replacement (PHR), and site of primary tumour were similar in each group. No major complications or side effects were noted. The follow up period ranges from 12-50 months. The median survival time in months from diagnosis are: control 10, HAE 8.5, and HA1 12.9. The median survival of the patients with a PHR <50% undergoing HA1 was 21.5 months compared with 8.2 months in the control group. A Cox’s proportional hazards model showed that age (p=0.02), PHR (p=0.001), and original Duke’s staging (p=0.01) are significant independent prognostic factors. Extra hepatic recurrence occurred in 35% of patients.

It seems likely that there is a slight survival benefit for HA1 especially with PHR <50%. The side effects are minimal. HAE offers no survival advantage in these patients.

Small bowel motor abnormality in slow transit constipation

D KUMAR, D WADDRON, N S WILLIAMS, AND D E WINGATE (Gastrointestinal and Surgical Units, London Hospital Medical College, London) In slow transit constipation (STC), abnormal colorectal motility has been reported, but it is not known whether other aspects of intestinal motor function are normal. We studied upper small bowel motility in 12 women with STC, aged 20–54 years, and who had 100% five day marker retention. Six healthy volunteers (H) with a normal bowel habit served as controls. Motor activity was recorded continuously for 24 hours using a fine (2-2 mm OD) probe introduced pernasally and positioned under fluoroscopic control with the tip in the proximal jejunum. The subjects were freely ambulant during the study. The incidence of phases I–III of the migrating motor complex (MMC) was analysed from the replayed records. The MMC incidence was similar in both groups during the day, but in the STC group, the interval between phase IIIs was significantly (p<0.001) shorter during the night (mean (SEM) intervals in minutes: STC – 37 (5.9), H – 64 (6.3)). The percentage of recording time occupied by phase II was significant (p<0.001). Calculation of a motility index (MI) for 30 minute epochs of phase II activity (poled day and night data) showed a significantly (p<0.02) increased MI in STC (14.2 (1.7)) compared with H (6.3 (0.8)). Thus, upper small bowel motor activity in STC is noticeably abnormal, with greatly increased phase II activity, and a considerable increase in MMC incidence during sleep.

These data suggest that STC may be the outcome of a panenteric motor disorder.

Cellular hypersensitivity in coeliac disease to synthetic peptides from shared epitopes in A-gliadin and adenosivus 12

GJ MANTZARI, JA KARAGIANNIS, JD PRIDDLE, AND DP JEWELL (Gastroenterology Unit, St Mary’s Hospital, Radcliffe Infirmary, Oxford) The adenosivirus 12 may be implicated in the pathogenesis of coeliac disease by immunological cross reactivity between its E1B protein (residues 384–395) and A-gliadin (residues 206–217). Cellular immune responses to these synthetic peptides have been studied in 12 treated coeliac patients and 12 healthy subjects. Both dodecapeptide sequences were synthesised by solid phase methods. Indirect leucocyte migration inhibition and proliferation assays were performed con-
currently using peripheral blood mononuclear cells (antigen concentrations 33.3, 11.1, 5.55 μg/ml). The release of migration inhibition factor was assayed by its effect on the migration under agarose of polymorphonuclear cells from healthy donors. The proliferation of sensitised lymphocytes was measured by H-thymidine incorporation. Results are expressed as migration and stimulation indices.

Using 33.3 μg/ml, the median migration indices for the viral and gliadin peptides respectively were 0.8 (0.6–1.10) and 0.76 (0.6–0.96) for the coeliac, and 1.13 (0.81–1.56) and 1.06 (0.92–1.40) for the control group. The differences were significant (p<0.001). The stimulation indices were 1.78 (1.01–4.50) and 2.4 (1.2–6.0) for the coeliac, and 0.9 (0.6–1.37) and 0.9 (0.58–1.13) for the controls (p<0.001). A dose response was seen in both assays. There was a highly significant correlation between the migration and the stimulation indices.

Thus, coeliac patients exhibit cellular immune responses to both gliadin and viral epitopes.

### Role of A-gliadin antibody assay in coeliac disease follow up

C P Kelly, D P Nunes, F Daly, C F Feighery, and D G War (Depts of Clinical Medicine and Immunology, Trinity College and St James’ Hospital, Dublin) Measurement of serum anti-gliadin antibody values is now a recognised screening method for coeliac disease. The aim of this study is to determine the role of anti-gliadin assay in patient follow up.

Seventy one coeliac patients were assessed over a three year period. Dietary status, serum IgA, and IgG anti-gliadin (by ELISA) and small intestinal biopsy histology were studied. Anti-gliadin antibody values were also measured in normal controls (n=40) and in patients with Crohn’s disease (n=35).

Serum IgA anti-gliadin assay showed a sensitivity of 87% and a specificity of 91% in detecting untreated coeliac disease. The sensitivity and specificity of the IgG assay were 78% and 84% respectively. Both IgA and IgG anti-gliadin were lower in treated than untreated patients (p<0.001). Coeliac patients who did not comply with dietary treatment showed no fall in serial antibody values. IgA anti-gliadin dropped to a baseline value within six months of commencing the diet. IgG anti-gliadin showed a more gradual, progressive decline and did not reach a baseline until patients had been on the diet for over 18 months. Anti-gliadin antibody values correlated more closely with dietary status (r=0.50) than with histological grading (r=0.32). Six patients continued to show noticeable histological abnormality despite good dietary adherence. Serum IgA and IgG anti-gliadin fell to low values in these ‘non-responsive’ coeliac patients.

Serum IgA anti-gliadin measurement is superior to IgG in screening for coeliac disease. It is also more useful in patient follow up as it provides an early, objective indicator of compliance with gluten free diet. In treated coeliac disease serum anti-gliadin antibody values reflect dietary adherence rather than mucosal response.

### Idiopathic bile acid malabsorption, an eight year experience of 60 patients

A J K Williams, M V Merrick, and M A Eastwood (Depts of Gastroenterology and Nuclear Medicine, Western General Hospital, Edinburgh) Diarrhoea as a result of idiopathic bile acid malabsorption is regarded as rare. We have reviewed 60 such patients seen in an eight year period to determine the characteristics of this condition and its response to treatment. Bile acid malabsorption (BAM) was defined as retention of less than 15% of administered "S"ICAT at seven days. All patients had normal "Co-B12 absorption, jejunal biopsy, brush border enzymes, and barium follow through.

Altogether 23 patients had severe BAM (0–5% retention). Age range 17–77 years (median 42), 10 male; 13 female. Duration of symptoms one month to five years. They had episodic moderate to severe water diarrhoea (4–12 motions/24 hours), nocturnal, with large stool volumes (400–800 g). All improved with bile acid chelators (cholestyramine, or aluminium hydroxide) with reduction in stool frequency and have remained well on therapy (six months to five years follow up).

A total of 21 patients had mild BAM (10–15% retention). Age range 13–72 years (median 30), eight male, 13 female. They had symptoms typical of IBS (watery diarrhoea in morning alternating with constipation, bloating), duration one to 25 years, and none improved with bile acid chelators.

Some 16 patients had moderate BAM (5–10% retention) and a proportion (six) were improved symptomatically with cholestyramine.

Severe BAM has characteristic clinical features which consistently improve with specific treatment.

### Increased risk of colorectal neoplasia after truncal vagotomy

F J Mullan, H K Wilson, C W Maulry, J M Mills, A Crombie, and S T McMullen (Dept of Surgery, Queen’s University, Belfast and Dept of Radiology, Ulster and Royal Victoria Hospitals, Belfast) An increased risk of colorectal cancer has been reported in retrospective studies of late mortality after vagotomy for peptic ulceration.

We have undertaken a prospective study of 100 asymptomatic individuals who had undergone truncal vagotomy 10 or more years previously. All were aged 50 years or more. They were screened by double contrast barium enema. Colonoscopy was performed in patients with suspicious lesions or suboptimal enema examination. Gall bladder status was established by ultrasonography. Control data were obtained from 100 subjects undergoing forensic necropsy examination matched as closely as possible for age, sex, and gall bladder status.

Eighty males and 20 females (mean age 63±0.2 (63–76) years) were studied a mean interval of 16±0.8 (3–7) years after truncal vagotomy. Some 25 patients had cholelithiasis and a further six had undergone cholecystectomy. Fourteen post-vagotomy patient’s had neoplasms ≥1 cm (11 had adenomatous polyps, three had carcinomas). In the control group three patients had adenomas ≥1 cm, none had carcinoma. This difference is significant (p<0.05 X 2).

We conclude that there is an increased risk of colorectal neoplasia a decade after truncal vagotomy and this group may merit screening.