Gut, 1976, **17**, 385-402

The British Society of Gastroenterology

The spring meeting was held at the University of Canterbury on 9 and 10 April 1976. On Friday morning a symposium on alcoholism was held with Dr M. O. Rake in the Chair. The speakers were Professor W. I. N. Kessel, Dr F. Sexias, Dr E. B. Ritson, and Dr B. D. Hore. The Spring Meeting Banquet was held at Eliot College, University of Canterbury, on Friday evening. Also on Friday afternoon and on Saturday morning there were sessions devoted to scientific papers on 'The pancreas' (Chairman: Dr L. M. Blendis), 'The small intestine' (Chairman: Professor C. C. Booth), 'The H_2 receptor antagonists' (Chairman: Dr K. G. Wormsley), 'The liver' (Chairman: Professor M. S. Losowsky), 'Inflammatory bowel disease' (Chairman: Professor J. C. Goligher), 'Polypeptide hormones' (Chairman: Professor E. L. Blair), 'The biliary tract and liver' (Chairman: Professor I. A. D. Bouchier), 'The stomach' (Chairman: Professor H. L. Duthie), 'The small intestine' (Chairman: Dr G. E. Sladen), 'Inflammatory bowel disease' (Chairman: Professor L. A. Turnberg), and 'The stomach' (Chairman: Dr J. Rhodes). Abstracts of the papers presented to the Society follow.

The trypsin inhibitory activity of pure human pancreatic juice

E. ELIAS, J. SOUTHCOTT, A. MARTEN, J. SCOTT, J. A. SUMMERFIELD (*Department of Medicine, The Royal Free Hospital, Pond Street, London NW3*) Pancreatic juice has been collected from within the pancreatic duct after i.v. secretin at ERCP and its trypsin inhibitory activity, total trypsinogen content, trypsin and protein concentration measured.

Patients included 17 with a normal pancreas (11 non-alcoholic [control group]; 6 alcoholic), 9 with chronic pancreatitis (7 alcoholic, 2 non-alcoholic), 5 with choledocholithiasis and 6 with recent acute pancreatitis. Activation of trypsinogen was significantly increased in choledocholithiasis ($P < 0.025$), in all alcoholics ($P < 0.05$) and in chronic pancreatitis ($P < 0.025$). The ratio of trypsin inhibitor to trypsinogen was significantly increased in chronic alcoholic pancreatitis ($P < 0.05$), in acute pancreatitis ($P < 0.025$), and in alcoholics without pancreatic disease ($P < 0.025$). No inhibitor activity was detected in 2 patients with non-alcoholic chronic pancreatitis. The protein concentration of pancreatic juice tended to be raised in alcoholics ($0.10 > P > 0.05$), so that the specific activity of inhibitor was not significantly raised except after recovery from acute pancreatitis ($P < 0.05$).

An increased ratio of trypsin inhibitor to trypsinogen in pancreatic juice is associated with alcoholism and antecedes clinically evident pancreatic disease. Deficiency of inhibitor may be associated with non-alcoholic chronic pancreatitis. Premature intraduct activation of trypsinogen occurs in alcoholism and choledocholithiasis. Increased trypsin inhibitor secretion occurs following acute pancreatitis.

Specificity of the renal amylase: creatinine clearance ratio in the diagnosis of acute pancreatitis and in detecting the incidence of pancreatitis after ERCP

A. MARTEN, E. ELIAS, J. A. SUMMERFIELD, J. SCOTT and S. SHERLOCK (*Department of Medicine, The Royal Free Hospital, London NW3*) The instantaneous renal amylase: creatinine clearance ratio (R) has been advocated as a simple, sensitive and specific test for the diagnosis of acute pancreatitis.[1]

In 64 control subjects R was 3.03 ± 0.09 (mean $\pm$ 1 SEM), range: 1·23-4·19. In 11 patients with acute pancreatitis diagnosed by history of abdominal pain, hyperamylasaemia and hyperamylasuria R was increased to 8.56 ± 0.27 (range: 6·76-9·81, $P < 0.001$). In 9 patients with chronic pancreatitis without diabetes R was 3.26 ± 0.26 (NS), but was increased in 10 patients with diabetes mellitus (4.95 ± 0.53, $P < 0.001$)[2] though their serum amylase was subnormal ($P < 0.05$). R was also increased in 4 patients with choledocholithiasis though 3 of these had a normal serum amylase. A normal R with hyperamylasaemia has been found in chronic renal failure. Of 81 patients having ERCP, R increased from normal to 6·76, 10·32 and 9·62 respectively in 3 patients (3·7%) in whom there was clinical evidence of acute pancreatitis. However in 15 (18·5%) other patients in whom asymptomatic hyperamylasaemia followed ERCP, R was not elevated. An elevated R is highly suggestive of acute pancreatitis even in the absence of hyperamylasaemia if diabetes mellitus is excluded. A normal R in the presence of hyperamylasaemia makes pancreatitis unlikely.

References

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[2] Levine, R. I., Glauser, F. L., and Berk, J. E. (1975). Enhancement of the amylase-creatinine clearance ratio in disorders other than acute pancreatitis. *N. Eng. J. Med.*, **292**, 329-332.

Chronic pancreatitis: a cause of cholestasis

J. SCOTT, J. SUMMERFIELD, E. ELIAS, R. DICK AND S. SHERLOCK (*Departments of Medicine and Radiology, The Royal Free Hospital, London NW3*) Cholestasis is not well recognised as a complication of non-gallstone chronic pancreatitis. In a series of 6 patients investigated for cholestasis by endoscopic retrograde cholangiopancreatography and Chiba needle percutaneous cholangiography non-gallstone pancreatitis was shown as the sole cause of biliary stricture and cholestasis. Thirty-two further patients presenting consecutively with non-gallstone chronic pancreatitis were therefore studied to establish the frequency of biliary

stricture with or without cholestasis. Five of these 32 patients (16%) had biliary complications.

Ten of the 11 patients with biliary complications had experienced previous episodes of transient cholestasis during exacerbations of chronic pancreatitis. Six patients eventually developed persistent cholestasis requiring surgery. One patient had biliary stricture, but had never experienced cholestasis. Stenosis of the intrapancreatic distal common bile duct was the anatomical basis of both transient and persistent cholestasis. Pancreatic carcinoma was not found in the 6 surgical patients. This was confirmed at autopsy in one patient. Three of these 6 patients remain well eighteen months and 3 twelve months after surgery. In 10 of the 11 patients with biliary complications pancreatitis was of alcoholic aetiology.

It is concluded that cholestasis is a common, but poorly recognised, complication of non-gallstone chronic pancreatitis, especially when severe and due to alcohol.

The significance and management of arterial hypoxia in acute pancreatitis

C. W. IMRIE, J. C. FERGUSON, D. MURPHY, I. MACKENZIE, J. F. DAVIDSON AND L. H. BLUMGART (*University Department of Surgery, Centre for Respiratory Investigation and Department of Haematology, Glasgow Royal Infirmary*) Daily arterial blood gas measurements (ambient air) in 129 patients with acute pancreatitis has revealed severe hypoxia (paO_2 < 60 mm Hg) in 43% and moderate hypoxia (paO_2 < 70 mm Hg) in 74% of patients. The overall mortality rate was 7·8% (10 deaths) and an association with hypoxia was found. This association between prognosis and the degree of hypoxia was not found in a previous study where arterial blood gas measurements were confined to the initial 48 hours of illness[1]. In the present study measurements were continued for a minimum of 5 days after hospital admission. A level of paO_2 above 85 mm Hg was usually achieved by the provision of humidified oxygen via a Hudson mask at 4-10 l/min. but in occasional patients albumin and frusemide therapy was required ± mechanical ventilation.

Additional extensive respiratory investigations have been performed in 17 of these patients and indicate a multifactorial mechanism for the arterial hypoxia. Daily chest radiology showed pleural effusion, atelectasis or pulmonary oedema in a majority of this sub-group and a significant veno-arterial shunt (5-28% of cardiac output) with elevated FDP levels in 14 cases.

Reference

[1]Ranson, J. H. C., Turner, J. W., Roses, D. F., *et al.* (1974). Respiratory complications in acute pancreatitis. *Ann. Surg.*, **179**, 557-566.

Hypocalcaemia of acute pancreatitis: the effect of hypoalbuminaemia

C. W. IMRIE, B. F. ALLAM, J. C. FERGUSON AND L. H. BLUMGART (*University Departments of Surgery and Pathological Biochemistry, Glasgow Royal Infirmary*) In a prospective study of 130 patients with acute pancreatitis, 64·4% of the serum calcium results in the initial two weeks of hospitalisation were hypocalcaemic. A comparable incidence of hypoalbuminaemia was observed and the total serum calcium and serum albumin figures showed significant correlation in their daily variations. When the serum calcium was corrected for the hypoalbuminaemia only 10·9% of all serum calcium results were below 2·2 mmol/l, and 4.2% below 2·0 mmol/l. Mortality and severity of acute pancreatitis related as closely to hypoalbuminaemia, as to uncorrected hypocalcaemia. Serum globulin results remained within the normal range indicating that haemodilution was not a major factor in the hypoalbuminaemia. Aspirates of peritoneal and pleural effusion fluid had a high albumin content (> 28 g/l) and it is proposed that redistribution of albumin within various body compartments is a major factor in this hypoalbuminaemia.

The cause of hypocalcaemia in acute pancreatitis has remained largely unresolved for over 30 years[1]. Calcium deposition as 'soaps' and hyperglucagonaemia are now considered inadequate explanations and more recently parathyroid gland failure has been implicated[2]. Hypophosphataemia[3] is attributable to decreased renal tubular reabsorption of phosphate shown in our current series of patients indicating enhanced PTH activity in acute pancreatitis. Finally, ionised calcium levels in 15 patients with acute pancreatitis are consistent with the theory that a low serum albumin is the most common cause of hypocalcaemia in acute pancreatitis.

References

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[3]Imrie, C. W. and Whyte, A. S. (1975). A prospective study of acute pancreatitis. *Brit. J. Surg.*, **62**, 490-494.

Stimulation of intestinal cyclic AMP by a heat stable toxin of *Escherichia coli* 0148

N. EVANS, P. J. TURNER, G. A. BROWN, AND A. S. MCNEISH (*Institute of Child Health, Francis Road, Birmingham*) Pathogenic strains of *Escherichia coli* possessing the Ent^+ plasmid may produce one or two soluble enterotoxins[1]. The lower molecular weight, heat stable component (ST) has been implicated in travellers' diarrhoea[2], but its mode of action is unknown. By contrast the heat labile component (LT) is known to behave like cholera toxin and to stimulate adenylate cyclase in many tissues with a secondary rise in cyclic 3'5' adenosine monophosphate (cyclic AMP). We have developed an assay system utilising human foetal jejunum in organ culture that suggests that ST may also activate adenylate cyclase.

Toxin was prepared from *E. coli* 0148 K? H28 isolated from soldiers in Aden[3]. Non-pathogenic controls were included throughout. After concentration and division into fractions by ultrafiltration, the toxin was incubated with pieces of human foetal intestine. The foetal tissue was then homogenised and the cyclic AMP measured by a competitive protein binding assay.

Low molecular weight fractions were shown to stimulate cyclic AMP within the first two hours of incubation. These cyclic AMP peaks were earlier and lower than the stimulation produced by cholera toxin. The fractions were stable to heating.

It is concluded that ST stimulates intestinal adenylate cyclase; this may have important therapeutic implications.

References

[1]Smith, H. W. and Gyles, C. L. (1970). The relationship between two apparently different enterotoxins produced by enteropathogenic strains of Escherichia coli of porcine origin. *J. Med. Micro.*, **3**, 387-401.

[2]Sack, D. A., Merson, M. H., Wells, J. G., Sack, R. B., and Morris, G. K. (1975). Diarrhoea associated with heat stable enterotoxin producing strains of Escherichia coli. *Lancet*, **ii**, 239-241.

[3]Rowe, B. Taylor, J., and Bettelheim, K. A. (1970). The investigation of travellers' diarrhoea. *Lancet*, **i**, 1-5.

Patterns of small intestinal permeability and the effect of hypertonic solutions

P. G. WHEELER,* I. S. MENZIES, AND B. CREAMER (*Gastrointestinal Laboratory,*

St. Thomas's Hospital, London SE1) Intestinal permeability to a large range of molecular sizes is now an established fact, particularly to protein-sized molecules[1]. This study provides evidence for permeability in the medium range.

A group of normal fasting individuals were given oral loading solutions consisting of lactulose 5 g (disaccharide MW 342), raffinose 5 g (trisaccharide MW 504) stachyose 5 g (tetrasaccharide MW 666), and 1 g fluorescein isothiocyanate-labelled dextran of very narrow molecular weight range (mean 3000), in water. These oligosaccharides are non-hydrolyzed, non-actively absorbed, and rapidly and completely excreted in the urine following intravenous injection. The amount in the urine following an oral load thus reflects that which has crossed the intestinal mucosa. A five hour urine collection was made and prepared for accurate estimation of the individual saccharide content by the quantitative paper chromatography technique described by Menzies[2]. The FITC-Dextran content was measured by a spectrophotofluorometric method. Similar experiments were also carried out with hyperosmolar solutions containing added glycerol to an osmolarity of 2000 mOsm/L.

The mean percentage urinary recoveries (± SE) in twelve individuals following an oral isosmotic load are: lactulose: 0·205% ± ·02, raffinose: 0·129% ± ·01, stachyose: 0·097% ± ·01, FITC-dextran 3000: 0·039% ± ·004. The difference between all these is significant ($P < ·001$).

For increasing molecular weight there is decreasing recovery, or intestinal transfer, of these substances. Being very hydrophilic with negligible lipid solubility, it is likely that they traverse the intestinal wall via an aqueous route, presumably water-filled pores, and possibly via a tight-junction pathway. The difference in transfer between substances may be due to differences in simple aqueous diffusion and this can be allowed for by dividing each value by the diffusion coefficient of the substance concerned. This still gives values which decrease significantly with increasing molecular weight, therefore representing a profile of true permeation, with evidence of restriction by the pores in question with rising molecular size. Hyperosmolar loads produce an approximately five-fold increase in total recovery with a change in profile indicating an increase in mean effective pore size. The data will be presented and the significance discussed of this slight but real absorption of large molecules.

References

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Measurement of the functional unstirred layer thickness in the human jejunum in vivo

N. W. READ, R. J. LEVIN, AND C. D. HOLDSWORTH (*Departments of Medicine and Physiology, University of Sheffield*) We have previously found that the operational kinetic parameters for the active electrogenic component of glucose absorption are significantly lower in patients with untreated coeliac disease than in healthy controls, but return to levels near the control values after treatment by gluten withdrawal[1]. These changes could be caused both by alterations in the transport mechanism itself or differences in the apparent thickness of the unstirred layer.

We have devised a method for estimating the unstirred layer thickness in man *in vivo* by measuring diffusion potential difference (PD) half times during experiments to determine kinetic parameters for electrogenic glucose absorption. Using this technique we have found that the apparent unstirred layer thickness in six patients with untreated coeliac disease (487 ± 8 μm; mean ± 1 SEM) was significantly lower than in seven healthy controls (617 ± 22 μm), but in five patients with treated coeliac disease it was virtually identical to the control value (605 ± 67 μm).

Such differences in unstirred layer thickness could account at least in part for the reductions in apparent Km and PD max for glucose in patients with untreated coeliac disease. However because of the presence of the unstirred layer, the decreases in the maximal rate of glucose absorption (Jmax) previously found in untreated coeliac disease[2] could also produce similar changes in both the operational parameters.

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[2]Holdworth, C. D., and Dawson, A. M. (1965). Glucose and fructose absorption in idiopathic steatorrhoea. *Gut*, **6**, 387-391.

Transit time measurements: Is a new method required?

J. H. CUMMINGS, D. J. A. JENKINS, AND H. S. WIGGINS *MRC Gastroenterology Unit, Central Middlesex Hospital, London, NW10*) Transit through the gut may be measured by giving a single dose of marker to a subject and measuring the excretion of 80% in the stool (80% TT)[1]. With this technique we have measured transit on three successive days using different but comparable markers on each day in 15 normal subjects on 40 occasions. Wide variations in transit time amongst the three doses of marker in each subject were found (coefficient of variation 26·3%). As such differences seemed unlikely to be due to biological variation alone we have developed a new method for measuring transit.

A constant number of radio-opaque markers are fed to a subject (5 per meal, 15 per day) for several weeks and their excretion in the stool measured. The number of markers retained in the gut at any time may be calculated from this and therefore the mean transit time (MTT). A continuous daily record of transit is obtained.

The 80% TT was compared on 50 occasions in 13 subjects with the MTT. The mean value for 80% TT was 63·1 h ± 3·0 SEM and for MTT over identical periods 54·2 h ± 2·5 ($P < 0·05$).

In 6 normal subjects who took the markers daily for 4 weeks the average MTT was 55 h (range 17-96 h). Some variation in MTT from week to week was noted.

In a further group of 6 subjects taking a controlled metabolic diet for six weeks to which cereal fibre was added for three weeks the 80% TT did not show a significant change between the two diets whereas the MTT showed a significant fall with added fibre.

Reference

[1]Hinton, J. M., Lennard-Jones, J. E., and Young, A. C. (1969). A new method for measuring gut transit times using radio-opaque markers. *Gut*, **10**, 842-847.

The use of an elemental diet, (Vivonex) in the management of bile acid-induced diarrhoea

L. NELSON, H. A. CARMICHAEL, S. T. ATHERTON, AND R. I. RUSSELL (*Gastroenterology Unit, Royal Infirmary, Glasgow, G4 0SF*) Bile acid-induced diarrhoea is a major problem in many patients with

Crohn's disease and after ileal resection, and is often difficult to treat satisfactorily[1]. We have studied the effect of a low-fat containing elemental diet (Vivonex) on faecal bile acid excretion, and in the management of patients with cholerheic diarrhoea.

Initial studies in rats over a 9 week period showed a consistently satistically significant reduction of total faecal bile acid excretion in rats treated with Vivonex compared with those on a normal diet. Thus, at 7 weeks the total faecal bile acid excretion (± SEM) in Vivonex-treated rats was 0·79 ± 0·9 mg/g dry weight faeces compared with 2·13 ± 0·17 mg/g in the control group ($P < 0·005$).

Eight patients with cholerheic diarrhoea were studied; 5 with ileal resection, 2 with severe Crohn's disease, and 1 with severe continuous post-vagotomy diarrhoea. The mean total faecal bile acid excretion (± SEM) in the group was 2447 ± 492 mg/day (range 860 to 4903 mg/day). On treatment with Vivonex a marked improvement in the diarrhoea occurred in all patients, the stools were better formed and less urgency noted. The total faecal bile acid excretion was significantly reduced during treatment with Vivonex (mean 1028 ± 327 mg/day; range 189 to 3229 mg/day; $P < 0·01$). The primary bile acids chenodeoxycholic acid and cholic acid were reduced during Vivonex therapy.

An elemental diet of this type may be of value in the management of patients with cholerheic diarrhoea unresponsive to other forms of therapy. This treatment has the additional advantage of offering a high nutritional diet which requires little digestion and which is easily assimilated[2]. This may be of particular importance in patients with Crohn's disease.

References

[1]Hofmann, A. F. (1967). The syndrome of ileal disease and broken enterohepatic circulation: cholerheic enteropathy. *Gastroenterology*, 52, 752.

[2]Russell, R. I. (1975). Elemental diets. *Gut*, 16, 638.

The effect of the histamine H_2-receptor on canine gastric mucosal barrier

G. KENYON AND D. C. CARTER (*Department of Clinical Surgery, Edinburgh University Medical School*) The histamine H_2-receptor antagonist, cimetidine, increases gastric mucosal potential difference in man and it has been suggested that it may protect the mucosal barrier in addition to suppressing acid secretion[1].

Na^+ and H^+ flux across the gastric mucosa were studied in vagally-denervated pouches in two antrectomised male dogs. Ion flux during exposure to a standard solution of 80 mM HCl made isotonic with NaCl, was compared with flux during instillation of cimetidine (200 mg in 20 ml standard solution). The rate of Na^+ output from the mucosa and the rate of H^+ back diffusion was not affected significantly by cimetidine.

In a second series of six experiments, 20 mM sodium taurocholate increased Na^+ output from +126 to +426·9 uEq/30 min ($P < 0·01$) and H^+ back diffusion from −62·2 to −647·0 uEq/30 min ($P < 0·001$). The flux of Na^+ and H^+ induced by taurocholate alone was not altered significantly when 200 mg cimetidine was added to the taurocholate in a further six experiments (Na^+ output +494·0 uEq/min; H^+ back diffusion −591·4 uEq/30 min).

It is concluded that while cimetidine does not disrupt the canine gastric mucosal barrier, the compound does not protect the barrier from the disruptive effect of 20 mM sodium taurocholate solution.

Reference

[1]Ivey, K. J.. Baskin. W., and Jeffrey, G. (1975). Effect of cimetidine on gastric potential difference in man. *Lancet*, ii, 1072-1073.

Role of histamine receptors in the pathophysiology of gastric mucosal damage

W. D. W. REES, J. RHODES, M. H. WHEELER, M. E. MEEK, AND R. G. NEWCOMBE (*University Hospital of Wales, Cardiff*) Bile acids damage the gastric mucosal barrier. We have examined the effect of histamine receptor antagonists (H_1 and H_2) on the changes which normally follow exposure of gastric mucosa to bile.

Four canine Heidenhain pouches were used to examine the damaging effect of sodium taurocholate, using a concentration which was just sufficient to produce consistent changes in each animal (12-20 mM). Pouches were exposed to solutions for thirty minute periods and changes in the volume, H^+ and Na^+ concentrations were measured. Before and after using the bile acid solution, the pouch was exposed to a solution which contained 100 mM HCl. During the four sets of experiments the dogs had an i.v. infusion of saline or saline with mepyramine maleate (10 mg/K, H_1) or metiamide (2 mg/K/h, H_2) alone or in combination. Four experiments were conducted in each animal with each infusion.

During the saline infusion, as well as with H_1 and H_2 infusions alone, similar results were obtained. With saline the bile produced a gain in volume (mean 0·7 ml) of the solution with a loss of H^+ (mean 150 uEq/30 min) and gain of Na^+ (mean 195 uEq/30 min) by the pouch. In contrast, during experiments where H_1 and H_2 antagonists were given in combination, the changes in volume and ionic flux were significantly reduced (means: vol −0·1 ml H^+ 68 uEq/30 min, Na^+ 96 uEq/30 min).

The results suggest that release of histamine and its subsequent action on receptor sites is responsible for the changes in ionic flux which follow exposure of gastric mucosa to bile.

The effect of cimetidine on lower oesophageal sphincter pressure in man

D. H. OSBORNE, J. LENNON, M. HENDERSON, G. LIDGARD, AND D. C. CARTER (*Department of Clinical Surgery, Edinburgh University Medical School*) Animal studies have suggested that the lower oesophageal sphincter (LOS) has histamine H_1 and H_2 receptors, and that metiamide raises LOS pressure by blocking inhibitory H_2 receptors and also augments the stimulatory effect of gastrin[1].

LOS pressures were measured every 15 minutes in sustained expiration and inspiration using a rapid pull through technique in six healthy male volunteers. Serum gastrin levels were measured every 15 minutes. Mean end-expiratory pressure varied from 30·4-31·5 mm Hg during a 45 minute basal period, falling to a lowest value of 22·5 mm Hg ($P < 0·05$) after 75 minutes of a 90 min infusion of the H_2 receptor antagonist, cimetidine (100 mg hr^{-1}). Corresponding values for end-inspiratory pressure were: basal variation 31·5-41·4 mm Hg, lowest value 27·0 mm Hg after 75 minutes of cimetidine ($P < 0·01$).

In six further experiments in 4 volunteers, pentagastrin (0·5 ug/kg I.V.) was injected rapidly before and after a 50 minute infusion of cimetidine (1·66 mg min^{-1}). Basal pressures did not differ significantly before and after cimetidine infusion. However, the mean highest pressure induced by pentagastrin was 64·6 mm Hg before, and 46·8 mm Hg after cimetidine infusion ($P < 0·05$).

It is concluded that cimetidine does not raise LOS pressure in man and does not augment the rise in sphincter pressure induced by pentagastrin.

Reference

[1]Cohen, S. and Snape, W. J., Jr. (1975). Action of metiamide on the lower esophageal sphincters. *Gastroenterology*, **69**, 911-919.

The prevention of relapse in duodenal ulceration by long-term nocturnal metiamide treatment

M. H. THOMPSON AND C. W. VENABLES (*Department of Surgery, Newcastle University*) metiamide has been shown to be an effective agent in the healing of duodenal ulcers when given for 28 days. Early experience suggested that relapse following withdrawal of the drug might be a major problem.

Seventeen patients with endoscopically-confirmed healed ulcers after a 28-day trial of metiamide entered a one-year double-blind trial of a single nightly dose of 400 mg metiamide compared with placebo. Patients were seen weekly, and endoscoped every 3 months, or when a symptomatic relapse occurred. Eight patients remained in the metiamide group and in the placebo group for analysis. Two in the former and 6 in the latter relapsed ($P = 0.66$). Analysis of the potential number of patient-weeks of remission compared with the number of patient-weeks of relapse revealed a significantly greater remission in the metiamide group ($P < 0.001$). There appeared to be a greater amount of duodenitis in the placebo group than in the metiamide group.

There were no subjective, haematological, or biochemical side-effects attributable to metiamide.

Continued nocturnal Metiamide appears to produce useful prophylaxis against ulcer recurrence.

A controlled trial of H_2^- receptor antagonists in prophylaxis of bleeding from gastrointestinal erosions in fulminant hepatic failure

R. J. BAILEY,* B. R. D. MACDOUGALL, AND ROGER WILLIAMS (*Liver Unit, Kings College Hospital, Denmark Hill, London SE5*) In a recently analysed series of patients with fulminant hepatic failure in grade 4 coma bleeding from gastrointestinal erosions constituted a major problem contributing to death in 54 of 105 patients. Since existing therapy was frequently unsuccessful in these patients and since gastric acid appears to be an important factor in the development of erosions we decided to carry out a controlled trial on the possible benefit of prophylactic administration of H_2^- receptor antagonists.

So far, of the 18 patients in the control group 10 have had profuse bleeding from either gastric or oesophageal erosions. In contrast, bleeding did not occur in any of the 12 who received metiamide or cimetidine at a dose of 150 mg intravenously to maintain an intragastric pH > 5. Statistical analysis shows this to be a highly significant difference ($P = 0.001$).

Thus, prophylactic use of H_2^- receptor antagonists appears to have an important place in the prevention of bleeding in patients with fulminant hepatic failure and perhaps in all patients who are susceptible to gastrointestinal erosions.

*R. J. Bailey was supported by The Canadian Hepatic Foundation.

C3 metabolism in HB_sAg positive and negative chronic active liver disease (CALD)

E. ELIAS, B. J. POTTER, H. C. THOMAS, AND S. SHERLOCK (*Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG*) It has been suggested that complement activation may be involved in the pathogenesis of chronic active liver disease (CALD). Since the plasma concentration of C3 is influenced by synthesis rate and catabolic rate, we have measured these variables in patients with HB_sAg positive and negative CALD.

Plasma concentrations of C3 were measured by radial immuno-diffusion, and C3 turnover by analysis of plasma disappearance curves of pure non-denatured radio-iodinated C3 and urinary excretion of radioactivity.

Plasma C3 concentrations were reduced in both HB_sAg positive and negative patients in accord with our previous studies[1].

In four HB_sAg positive patients the fractional and absolute catabolic rates for C3 were decreased. Similar changes were found in five untreated patients with HB_sAg negative CALD. However, one patient with HB_sAg negative CALD treated with prednisolone had a normal plasma concentration and slightly increased fractional and absolute catabolic rates of C3.

Our findings do not support the hypothesis that complement activation is involved in the pathogenesis of either HB_sAg positive or negative CALD. Decreased C3 synthesis may be secondary to liver injury or a primary defect in the complement pathway. The return to normal on treatment favours the first suggestion.

Reference

[1]Potter, B. J., Trueman, A. M., and Jones, E. A. (1973). *Gut*, **14**, 541.

Lymphocyte mediated cytotoxicity for Chang liver cells in acute and chronic liver disease

E. JACQUES, D. DE VILLIERS, H. C. THOMAS, AND S. SHERLOCK (*Department of Medicine, Royal Free Hospital, London, NW3 2QG*) The presence of a mononuclear cell infiltrate in the liver in acute and chronic hepatitis suggests that lymphocytes mediate the tissue damage in these diseases. We have measured the *in vitro* capacity of lymphocytes to destroy Chang liver cells using a standard chromium^{51} release assay.

Cytotoxicity was markedly increased in acute type A and B hepatitis and HB_sAg + ve chronic active hepatitis (CAH), only slightly increased in HB_sAg − ve CAH, and normal in chronic persistent hepatitis, alcoholic hepatitis, drug induced hepatitis and primary biliary cirrhosis. In acute viral hepatitis the increased cytotoxicity was transient and in CAH prednisolone treatment caused a reduction in cytotoxicity.

Rosetting techniques were employed to characterize the cell type responsible for this increased cytotoxicity. E rosetting to remove lymphocytes with receptors for sheep erythrocytes (T cells) resulted in no significant change in cytotoxicity. EA rosetting with sheep erythrocytes coated with IgG antibody to remove Fc-receptor bearing cells from the population, resulted in almost complete elimination of cytotoxicity. Further studies in which immunoglobin bearing cells were removed using an anti-Fab cyanogen bromide activated Sephadex column, demonstrated that the cytotoxic cells did not bear surface immunoglobulin, and were therefore not B-lymphocytes.

These studies demonstrate that the increased cytotoxicity to Chang liver cells in acute viral hepatitis and CAH is dependent on a cell which has the characteristics of a K cell (non-T, Fc receptor bearing mononuclear cell without surface immunoglobulin.)

Controlled trial of D-penicillamine therapy in chronic active hepatitis

R. B. STERN, S. P. WILKINSON, AND ROGER WILLIAMS (*The Liver Unit, King's College Hospital, London, SE5*) To date, reports of D-penicillamine in the treatment of chronic active hepatitis have been anecdotal and uncontrolled. In the controlled clinical trial reported here, penicillamine was compared with prednisone. The 35 patients were randomly allocated and both groups (18 receiving D-penicillamine and 17 prednisone) were similar on entry to the trial with respect to age, sex, liver function tests, presence of cirrhosis and HB_sAg. In all patients the disease had already been brought under control with corticosteroids, and at the start of the trial period the serum bilirubin in all cases was $\leq$ 2·5 mg/100 ml and aspartate aminotransferase $\leq$ 150 IU/L. Criteria for stopping treatment included either lack of control of the disease process (serum bilirubin > 3·5 mg/100 ml; or an aspartate aminotransferase > 250 IU/L) or drug toxicity.

During the first year of the trial 9 patients in the D-penicillamine group had to have their treatment discontinued (2 due to lack of disease control and 7 due to side effects). This is to be compared with 6 patients in the prednisone group (4 due to lack of disease control and 2 due to side effects). Detailed statistical analysis of the liver function tests in the patients remaining in the trial at the end of the year period showed no significant differences.

Thus it would appear that D-penicillamine is unsuitable for routine use in chronic active hepatitis because of the high incidence of side-effects, but in those patients in whom corticosteroid therapy becomes inadvisable, penicillamine may be just as good in keeping the disease under biochemical control.

Hepatoma in chronic liver disease

N. KRASNER, P. JOHNSON, A. BOMFORD, A. L. W. F. EDDLESTON AND ROGER WILLIAMS (*The Liver Unit, King's College Hospital and Medical School, London*) There is considerable variation in the reported frequency of hepatoma in cirrhosis. In a recent analysis of 279 Caucasian patients dying of chronic liver disease over the period 1967 to 1975 we have found a striking difference in the incidence of hepatoma in males and females. The frequency was 52% of 179 males as compared with 7% of 100 females ($P < 0·0005$). Age was also a significant factor. The incidence of hepatoma in those over 50 years was 30% but only 7% in those under 50 ($P < 0·0005$), this difference being independent of sex.

There was a close relationship between hepatoma and the male frequency in all the aetiological groups considered. The incidence of hepatoma was particularly high in three groups—alcoholic cirrhosis (30%), cryptogenic cirrhosis (32%) and idiopathic haemochromatosis (27%) and the number of males in each of these groups was also high, 65%, 70% and 95% respectively. In contrast, only one of the 33 patients with primary biliary cirrhosis died of hepatoma and there were only two males in this group. In chronic active hepatitis an intermediate frequency was found (18%) and here the sexes were equally represented. Although in this group hepatoma was commoner in the HB_sAg positive cases (38% compared with 11%), this again reflected a difference in the sex ratio (85% and 38% males respectively).

These results suggest that sex and age are of greater significance in the development of hepatoma than the aetiology of the underlying liver disease.

Asymptomatic primary biliary cirrhosis

R. G. LONG, P. J. SCHEUER, AND SHEILA SHERLOCK (*Departments of Medicine and Histopathology, Royal Free Hospital, London*) Routine biochemical and mitochondrial antibody testing is allowing primary biliary cirrhosis (PBC) to be diagnosed before hepatobiliary symptoms develop. Twenty-one such patients with a mean age of 47 years have been diagnosed. Eleven presented with abnormal liver function tests, 5 with hepatomegaly, 2 with hepatosplenomegaly and 1 each with Sjogren's syndrome and a positive mitochondrial antibody. The diagnosis was established by a raised serum alkaline phosphatase, a strongly positive mitochondrial antibody and diagnostic or compatible liver histology on needle biopsy. Eighteen had a raised serum IgM.

Eight patients still have no hepatobiliary symptoms 2-10 years (mean 4·8 years) from diagnosis; 4 of these remain asymptomatic after 6-10 years. Eight patients became symptomatic after a mean of 2·1 years and have survived on average 4·4 years since diagnosis. Two patients died of liver failure and 1 from bleeding varices after a period of 6·7 years from diagnosis, 2.3 years of which were symptomatic. Two patients had no hepatobiliary symptoms and died from another disease 1 and 6 years after diagnosis.

It is concluded that patients diagnosed as asymptomatic PBC may remain symptom free for many years. After becoming symptomatic the prognosis is similar to patients diagnosed when they present with symptoms.

Percutaneous, transhepatic catheterization and sclerosis of bleeding varices

J. SCOTT, R. LONG, R. DICK, AND S. SHERLOCK (*Departments of Medicine and Radiology, The Royal Free Hospital, Pond Street, London NW3*) Emergency surgical treatment of bleeding gastro-oesophageal varices in patients with cirrhosis has a very high mortality. An alternative treatment is percutaneous transhepatic catheterization of the portal vein with sclerosis of the major supply to the varices.[1,2]

This technique has been used in 11 poor-risk patients with cirrhosis and bleeding varices documented by endoscopy and angiography, in whom surgery was contraindicated. In 10 patients a transhepatic catheter was introduced into the portal vein; a portal venogram was obtained and portal pressure was measured. One patient had a previously undiagnosed portal vein block. In 5 patients the left and short gastric veins were selectively catheterized and sclerosed using hypertonic glucose and human thrombin. This was confirmed angiographically.

Two of the 5 successfully sclerosed patients had not recanalised at 3 months. One rebled after 10 days and splenovenography showed incomplete variceal occlusion. One has not yet been reassessed. The fifth patient died from bleeding hepatic puncture wounds. Complications included haemothorax (5 patients) and haemoperitoneum (2 patients).

This technique seems an advance in the treatment of bleeding varices in poor-risk patients with cirrhosis.

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A simpler, cheaper, more effective, safe method for removal of ascites

OLIVER JAMES, M. WARD, AND N. HOENICH (*Departments of Medicine (Geriatrics) and Medicine, University of Newcastle upon Tyne*) Recently an automated ultrafiltration device (Rhodiascit) has been described for rapid, safe removal of ascites[1,2]. The apparatus is costly and may be used infrequently in a general hospital. In the present method standard equipment available in district hospitals for peritoneal dialysis has been used to ultrafilter ascitic fluid and concentrate the protein before reinfusion of the concentrate intravenously.

Ascites is removed via a peritoneal dialysis catheter passed via a Watson Marlow M.H.R.E. pump and Avon R.322 arterial line across an acrylopolynitrile dry renal dialysis membrane (Rhone Poulenc R.P. 6) at a pressure of 250 p.s.i. (permeable below M.W. 25,000). The concentrate is passed via Swank cell filter (Extracorporeal Ltd.) and into sterile bottles for intravenous infusion.

Reinfusions have been carried out on 10 patients: 7 patients with liver disease resistant to diuretics, 1 tuberculous peritonitis, 2 malignant ascites. 3-8 litres were removed in 1-4 hours. No mechanical or medical complications arose except slight pyrexia in 2 subjects. Concentration of protein was 3:1 after ultrafiltration. The advantages of this method are cheapness and simplicity. Because of high transmembrane pressure, ascites of high protein content may be filtered.

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Inflammatory disease of the large bowel in children

DAVID CAIRNS (introduced by J. J. MISIEWICZ) and H. H. NIXON (*The Hospital for Sick Children, Great Ormond Street, London WC1*) Thirty-three children with ulcerative colitis and 15 with Crohn's disease, involving the large bowel were treated from 1946-1975. They presented shortly after birth and up to 12 years. The diagnosis was confirmed by radiological or histological means.

Ulcerative colitis presented with diarrhoea and rectal bleeding. But Crohn's disease presented as failure to thrive, malaise or poor appetite. Eleven had anal lesions, 3 had clubbing and 5 later had a mass in the right iliac fossa. Eight with ulcerative colitis had psychiatric problems and four from each group had affected relatives. Salazopyrine, systemic or rectal steroids were variously exhibited. Eight had a colectomy and IRA for ulcerative colitis and four colectomy, ileostomy with secondary excision of the rectum with 1 death; no case needed emergency colectomy. For Crohn's disease five had a right hemicolectomy of varying extent, one a colectomy and ileostomy, two colectomy and IRA, and one IRA was converted to ileostomy.

There have been no cases of carcinoma. Since surgery for ulcerative colitis and Crohn's disease all have gained much weight restoring them to their normal weight percentile and all are in excellent health. (Average follow up 8 years.)

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The continent colostomy

D. A. GRIFFITHS, E. PHILPOTTS, H. J. ESPINER, AND W. K. ELTRINGHAM (*Royal Infirmary, Bristol*) There are over 100,000 patients with colostomies in the United Kingdom. Each year a further 5,000 join them and present problems of long term management for the physician and surgeon. A recent survey found that over fifty per cent of colostomates expressed dissatisfaction with their colostomy and appliance[1]. The main complaints were odour, irregular action and loose motionn These complaints were compounded iy patients wearing unsatisfactory colostomy bags and who relied upon the natural action of the colon.

Regulation of colostomy action can be achieved by stimulating colonic activity with fluid distension. This method, called stoma cone irrigation, was offered to thirty-three patients with colostomies following abdomino-perineal excision of the rectum. Twenty patients expressed dissatisfaction with their colostomy appliance and received instruction in the use of the irrigation method. They were assessed at one week, three months and one year. Eighteen patients were delighted with the irrigation method and have continued to use it as the sole means of colostomy control. They found that the most convenient time for colostomy irrigation was the late evening. Instillation of two to three pints of tepid water, into the colon through the stoma cone produced vigorous colonic activity. The effluent was collected over a period of thirty minutes in a drainage bag and then discarded. Each patient was then free from further bowel actions for periods up to 48 hours. No complications were found and this method is recommended as a safe procedure for colostomates unhappy with their normal colon rhythm.

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The incidence and nature of sexual problems among married ileostomists

W. R. BURNHAM, J. E. LENNARD-JONES, AND B. N. BROOKE (*St. Mark's Hospital, London and St. George's Hospital, London*) The Ileostomy Association of Great Britain and Ireland has conducted a survey to assess the incidence and nature of sexual problems among a one in ten sample of its membership. The following results are based on the replies of 303 married ileostomists whose operation was performed for colitis. Twenty-four of 128 men and 21 of 175 women married after construction of the ileostomy: 39 of 118 men and 16 of 165 women had children after ileostomy and rectal excision.

Construction of an ileostomy, without rectal excision, did not lead to sexual dysfunction and only 8% of the sample found that the stoma caused any physical problem during intercourse. A sense of embarrassment or decreased sexual attractiveness was mentioned by 30% of the ileostomists but this did not appear to have affected their marriage. However, 10% of the total attributed some marital tension, and 2% attributed marital breakdown, to the stoma. Asked to choose an adjective 5% of the ileostomists chose the word 'repulsive' to describe the stoma rather than less emotive terms.

Removal of the rectum resulted in sexual dysfunction for 29% of the men. Among 61 men up to 35 years of age, five experienced partial and none experienced total erectile impotence; however, nine of the 61 had ejaculatory impotence. In the age group 36-45, eight developed partial and one of 27 men total erectile impotence. Over the age of 45 years, 11 of 30 men experienced partial and five total erectile impotence. Some replies showed that function could improve for up to two years after operation.

Sexual dysfunction was not a problem among women after rectal excision, but 30% developed dyspareunia.

Yersinia enteritis and enterocolitis

G. VANTRAPPEN, E. PONETTE, K. GEBOES, AND P. BERTRAND (*University Hospital St. Rafaël, Leuven, Belgium*) In a 4 year period we observed 37 cases of yersinia enteritis or enterocolitis. The diagnosis was confirmed by isolation of *yersinia enterocolica* (YE) in all but one patient. Only 2 of the isolated strains were of serotype 9, all others of type 3. Abdominal pain and watery diarrhoea were the most prominent symptoms, occurring in 80% of the patients. An appendicitis-like syndrome was observed in 40%. Other symptoms included anorexia, weight-loss, nausea, vomiting, arthritis and erythema nodosum. The duration of symptoms before diagnosis varied from 1 or 2 weeks in 32 patients to several months in 5. The most typical radiological abnormalities were found in the terminal ileum and consisted of a coarse, irregular or nodular mucosal pattern and of images which suggested the presence of ulceration. Endoscopic observations in 13 patients with severe diarrhoea showed signs of colitis in 6 patients, aphtoid ulcers in the colon in 2 and larger ulcerations in the terminal ileum in 1 patient. On pathological examination ulceration and a non-specific acute inflammatory cell infiltrate were seen. Treatment with tetracyclines or chloromycetin resulted within 4 to 6 weeks in the disappearance of symptoms and signs. In only one patient the antibody titre remained high and symptoms and radiological abnormalities persisted for months in spite of treatment.

The prognosis of idiopathic proctitis and distal colitis

J. POWELL-TUCK, JEAN K. RITCHIE, AND J. E. LENNARD-JONES (*St. Mark's Hospital, London*) The course of a consecutive series of 219 patients with proctitis or "distal" colitis with a history of less than six months, first seen in the decade 1962-71 and followed to 1974/5, has been analysed by the actuarial method. Idiopathic proctitis, defined as inflammation confined to the rectum with an upper limit on sigmoidoscopy, was diagnosed in 90 patients. The remaining 129 patients had inflammation extending above the limit of the sigmoidoscope but a double contrast barium enema was either normal or showed any abnormality of the mucosa to be distal to the left iliac crest.

In the proctitis group there were four unrelated deaths; the expected mortality from all causes was 5·91. Among the patients with 'distal' colitis there were 18 deaths, four of which appeared to be related to the colitis; the expected number of deaths from all causes was 15·71.

Among the 90 patients with proctitis, extensive colitis was later observed in five patients and left-sided colitis in three patients; four of these patients required surgical treatment. The cumulative risk of extension proximal to the left iliac crest was $8 \pm 3\%$ at five years and $12 \pm 4\%$ at ten years. Among the 129 patients with 'distal' colitis, 13 patients subsequently developed extensive colitis, nine substantial and six left-sided colitis; nine of these patients required surgical treatment. The cumulative risk of extension was $14 \pm 3\%$ at five years and $30 \pm 5\%$ at ten years.

This study shows that when an upper limit of the disease was seen on sigmoidoscopy at the first attendance, the subsequent mortality was low but there was a risk of later involvement of the colon proximal to the sigmoid in at least 10% of patients. On the other hand, 'distal' colitis as defined above was associated with a mortality and a greater risk of left-sided or extensive colitis during the follow-up.

Intersphincteric excision of the rectum in benign inflammatory conditions

J. A. LYTTLE AND A. G. PARKS (*Departments of Surgery, Guy's Hospital and St. Mark's Hospital, London*) In excising the rectum for neoplastic conditions, wide excision is necessary. In benign inflammatory conditions this needlessly removes healthy pelvic musculature and may increase the risk of damage to pelvic nerves subserving sexual function. These nerves are at risk during ligation of the middle rectal arteries, traction on the lateral ligaments of the rectum and perineal dissection beneath the sacral fascia.

Other authors have emphasised the need for close dissection of the rectum[1], but this technique includes excision of the rectum and anal canal in the intersphincteric plane. This is the plane of fusion between the visceral rectum and anal canal and the somatic pelvic musculature.

Operation:
Abdominally, close dissection of the rectum, particularly in the region of the lateral ligaments, is carried down to the lower ampulla. Perineally, the intersphincteric plane is entered, using retractors as the dissection deepens, to join the abdominal plane. A suction tube drain is inserted.

Results:
Fifty-three cases are presented, thirty-nine with ulcerative proctocolitis, thirteen with Crohn's disease, and one of uncertain aetiology.

There was no operative mortality and post-operatively the pelvic muscles could be shown to contract normally by electromyography.

Perineal wound healing:
Despite an intact pelvic floor, the results compare well with other series[2], 59% of the ulcerative colitis cases being healed by six months and 85% by one year. In thirteen cases of Crohn's disease, the results were 38% and 54% respectively.

Sexual function:
Only one man, aged 54 years, of the fourteen men in whom information is available, showed partial dysfunction. Other authors suggest dysfunction in 0-25% of cases. Burnham[3] found 29% dysfunction in a large series of ileostomists.

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Simultaneous differentiation of gastrin, CCK, EG and VIP cells

J. M. POLAK, S. R. BLOOM, A. M. J. BUCHAN, AND A. G. E. PEARSE (*Departments of Histochemistry and Medicine, RPMS, London*) Recent advances in methodology are leading to a better understanding of gut endocrine physiology. It is clear that gastrointestinal function is under continuous hormonal regulation. Much work has been done on the dynamics of hormone release but little information has been available on the state of activity of the various hormone producing cells. This is due to difficulties which have now been overcome by the development of new techniques[1]. The distribution of many of the gut hormones overlaps and it is thus important to assess their cellular origin and precisely define the electron microscopical appearance of each cell type. This has now been achieved in respect of two overlapping

groups of hormones by applying immunocytochemistry to resin-embedded material.
1 Comparison of serial 1 μm sections of human small intestinal mucosa stained with highly specific separate antibodies to CCK and gastrin shows that the two peptides are located in different cells.
2 Similarly the distal intestinal hormones, enteroglucagon (EG) and vasoactive intestinal polypeptide (VIP), are conclusively shown to originate in separate cells.

The enteroglucagon cell has been shown to be completely separate from the A cell of the pancreas and gastric fundus of the dog, and to exist in only one, well-defined, morphological type. Enteroglucagon, despite its multiple circulating forms, is thus a single hormonal peptide produced by a single type of endocrine cell.

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Little gastrin response to a meal: A comparison between patients with duodenal ulceration and normal subjects

I. L. TAYLOR AND G. J. DOCKRAY (introduced by R. A. Gregory) (*Physiology Laboratory, University of Liverpool, Liverpool L69 3BX*) Two circulating forms of gastrin predominate postprandially, 'little gastrin' (G17) and 'big gastrin' (G34). At equimolar blood levels G17 is six times more potent than G34 in stimulating acid secretion, and its $T\frac{1}{2}$ is one sixth that of G34[1]. Patients with duodenal ulceration (DU) secrete more acid than normal; this could be due to an increased ratio of G17 to G34.

After a standard meal (eggs, toast and Oxo) circulating concentrations of G17 and G34 were compared in normal subjects ($n = 25$) and DU patients ($n = 25$). Concentrations were measured by radioimmunoassay using two antisera; one almost absolutely specific for G17, the other C-terminal specific and therefore measuring G17 and G34[2].

Peak G17 concentrations (20 min after feeding) were higher in DU patients (Δ G17 = 18 fmol/ml) than in normal subjects (Δ G17 = 13·5 fmol/ml) but the difference was not significant. However, peak concentrations of G34 in DU patients (30 min Δ G34 = 36·03 fmol/ml) was significantly higher ($P < 0.05$) than in normal subjects (40 min Δ G34 = 20·07 fmol/ml).

Because of the low relative potency of G34 the higher concentration in DU patients probably contributes minimally to their increased acid secretion.

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Release of antral gastrin by infusion of liver extract into the small intestine of dogs

M. R. THOMPSON, H. T. DEBAS, J. H. WALSH, AND M. I. GROSSMAN (introduced by I. E. Gillespie) (*University Department of Surgery, The Royal Infirmary, Manchester and V.A. Centre, Wadsworth, Los Angeles*) Recognized stimuli for release of gastrin include digested protein bathing the antral mucosa, distension of the stomach and vagal stimulation. An intestinal phase of antral gastrin release has not been previously demonstrated.

Three dogs (18 to 22 kg) were prepared with vagally innervated antral pouches and gastric fistulae. Liver extract which is known to release gastrin when it bathes the antral mucosa was infused into the small intestine via the gastric fistula and serum gastrin concentration measured under three conditions: (1) antral pouch filled with 0·15 m $NaHCO_3$, (2) pouch filled with 0·15 m HCl, and (3) following antrectomy. The solutions of 0·15 m $NaHCO_3$ or 0·15 m HCl were placed in the antral pouches 30 minutes before infusion of liver extract began and maintained at zero pressure. Infusion of liver extract caused a significant rise in the serum gastrin when the antral pouch was filled with either 0·15 $NaHCO_3$ or HCl. This was completely abolished by surgical removal of the antral pouch. These data show that there is an intestinal phase of antral gastrin release.

A remarkable feature of this form of antral gastrin release is that it is not abolished by antral acidification. The only form of gastrin release that has previously been shown to be resistant to inhibition by antral acidification is that produced by bombesin[1] suggesting that this intestinal phase of gastrin release may be mediated by a bombesin-like peptide.

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Secretin pharmacokinetics and plasma levels for half maximum bicarbonate response in man

W. H. HAECKI, D. BELOHLAVEK, S. R. BLOOM, L. DEMLING, W. DOMSCHKE, S. DOMSCHKE, C. GALARIOTIS, C. MALLINSON, P. MITZNEGG, AND E. WUENSCH (*Departments of Medicine, RPMS, Hammersmith Hospital and Greenwich District Hospital, London; Departments of Medicine and Pharmacology, University of Erlangen-Nurnberg and Max Planck Institute of Biochemistry, Munchen, W. Germony*) The hormone secretin, although potent pharmacologically, has still not been shown to be important in human physiology. Previous experiments by our group[1] have shown that drinking lemon squash releases secretin in significant amounts. In order to investigate the correlation to pancreatic response we infused pure synthetic secretin at different dose levels into normal volunteers for 60 minutes and measured pancreatic bicarbonate output by standard duodenal aspiration technique. Both infusion rates and plasma levels of secretin were measured by a specific radioimmunoassay sensitive to 1·5 pmol/l.

Metabolic clearance rate in 5 healthy volunteers was found to be 11·2 $\pm$ 1·3 ml/min/kg, the half life was 2·8 minutes and the apparent volume of distribution was 4·5% of body weight. Infusion rate of 0·25 pmol/min/kg produced a mean plasma secretin level of 22 pmol/l, similar to maximal levels after endogenous stimulation, and induced half maximum bicarbonate output.

It is concluded, therefore, that secretin at physiological plasma levels stimulates pancreatic bicarbonate juice flow and is therefore likely to play a major role in duodenal pH control.

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Radioimmunoassay of a new gut hormone—human pancreatic polypeptide

T. E. ADRIAN, S. R. BLOOM, M. G. BRYANT, J. M. POLAK, AND Ph. HEITZ (*Departments of Medicine and Histochemistry, Royal Postgraduate Medical School, Hammersmith Hospital, London*) A radio-

immunoassay has been set up for human pancreatic polypeptide (HPP), a new pancreatic hormone.

The fasting plasma HPP level in 25 subjects was 31·1 pmol/l (SEM ± 6·2). Plasma PP levels rose post-prandially in 7 subjects to a peak of 164 ± 46 pmol/l at 30 minutes and were still elevated six hours later 80 ± 26·5 pmol/l. In total pancreatectomy patients PP was undetectable.

In 5 primates the pancreas contained 93% of the total PP in the gut (123 ± 16 pmol/g). Histochemical studies in man demonstrated PP cells in small groups between pancreatic acinar cells. PP cells were detected in low concentration throughout the gastrointestinal tract but not in heart, lung or liver.

Plasma PP levels were markedly raised in 18 out of 28 patients with pancreatic endocrine tumours (> 300 pmol/l)[1]. Tumour tissue contained PP cells demonstrated histochemically and tumour extracts contained a high assayable PP content. High concentrations of PP were also present in hepatic and lymph node metastases demonstrating its primary production by the tumour tissue.

PP from pancreatic apudomas, a liver secondary and normal human and baboon pancreas were all indistinguishable from pure HPP in elution pattern from a high resolution calibrated gel column, only a single peak being detected.

Reference

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Dual role for vasoactive intestinal peptide—peripheral hormone and neurotransmitter

M. G. BRYANT, S. R. BLOOM, R. H. ALBUQUERQUE, J. M. POLAK, AND I. MODLIN (*Departments of Medicine, Histochemistry and Surgery, Royal Postgraduate Medical School*) The development of sensitive and specific techniques for measurement of peptide hormones has led to the discovery of previously well-characterised hormones in new, unpredicted locations.

We have previously shown that VIP occurs throughout the mammalian gut. In view of the postulated neural crest origin of endocrine cells, the brain and various other tissues have also been analysed for possible VIP content. Tissues were dissected from animals immediately after death, boiled for ten minutes and extracted with 0·1 m formic acid. The VIP content of the extracts was determined by specific radioimmunoassay. In all species studied, highest concentrations of VIP in the central nervous system were found in the cerebral hemispheres, with significant quantities being present in the pons, medulla, hypothalamus and spinal cord. VIP was also detected in adrenal and salivary glands, gall-bladder, bladder and kidney.

Column chromatography of the extracts, on Sephadex G50 superfine, has demonstrated that this VIP immunoreactivity elutes identically with the originally described pure porcine hormone.

The presence of VIP in the brain, throughout the gut and in certain other tissues, raises the question as to whether this peptide might also function as a neurotransmitter substance.

The influence of age on cholesterol saturation of bile

D. B. TRASH, P. E. ROSS, J. MURISON, AND I. A. D. BOUCHIER (*Department of Medicine, Ninewells Hospital, Dundee*) The presence of a lithogenic bile is said to predispose to cholesterol gallstone formation. A significant difference can be demonstrated in the lithogenicity of bile obtained from normal individuals and patients with gallstones[1], although it has been shown that bile obtained from individuals without gallstones is also supersaturated[2]. Results quoted[2] in support of this have not taken into account the age of the donor but have merely relied on the presence of a normal gallbladder.

We have considered five groups of individuals in the age ranges 15-29; 30-39; 40-49; 50-59; 60 and over. None of these subjects had ever had biliary tract disease. They fell into two categories: normal individuals or patients who had had a completely normal cholecystogram during investigation for abdominal symptoms.

Bile was obtained from these subjects by duodenal drainage and analysed for organic phospholipid cholesterol and bile acid content. From these data a lithogenic index[3] was calculated. This index shows a tendency to rise with increasing age and in the 15-29 age group it showed a highly significant difference ($P < 0.01$) from all other groups.

Nevertheless, the large majority of all bile samples were supersaturated when contrasted with presently accepted criteria of cholesterol solubility in bile[2].

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Lithocholate kinetics in patients ingesting chenodeoxycholic (chenic) acid for gall stone dissolution

ROBERT ALLAN AND A. F. HOFMANN (*Nutritional and Intestinal Unit, The General Hospital, Birmingham B4 6NH and The Mayo Clinic, Rochester, Minnesota, 55901, U.S.A.*) Chenic acid is effective for gall stone dissolution in many patients. Its ingestion in non-human primates induces marked hepatotoxic damage due to the accumulation of lithocholate, the principal bacterial metabolite of chenic acid. These observations have restricted its use in man though thus far its ingestion has not caused significant hepatotoxic damage. The aim of the investigation was to measure the amount of lithocholate absorbed and total lithocholate pool size in gallstone patients ingesting chenic acid. Labelled lithocholate was administered intravenously. Bile samples were obtained 5, 10, 15, 24, 36, 48 and 60 hours after injection, and aliquots retained for analysis. Radioactivity was measured and mass determined by gas chromatography. Specific activity decay curves were biexponential with a rapid first component. Input and exchangeable pool size were calculated using the Hamilton-Stewart equation[1]. Three patients and three healthy volunteers were studied. The mean lithocholate pool size in gall stone patients was 0·27 mM with a mean input of 0·47 mM per day, a fourfold increase when compared with healthy controls. The striking increase in lithocholate absorption in gall stone patients ingesting chenic acid has not been associated with significant hepatotoxicity suggesting that the metabolism of absorbed lithocholate is different in man from other non-human primates.

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Bile cholesterol saturation varies during the menstrual cycle

T. S. LOW BEER, A. C. B. WICKS, P. DURRINGTON, AND K. W. HEATON (*University Department of Medicine, Bristol Royal Infirmary, Bristol*) Women are more prone to develop cholesterol gallstones than men. If this is due to an effect of sex hormones, cholesterol saturation of bile, and therefore the gallstone risk, may vary in relation to the menstrual cycle. Twelve healthy women aged 20-43, each with a regular 26-30 day cycle, volunteered for a study of fasting bile cholesterol saturation. None had taken hormone preparations for at least three months. Fasting gallbladder bile was aspirated from the duodenum at the end of the menstrual bleeding (EB), at mid-cycle (MC), and 8-9 days later (PP), at the time of the expected progesterone peak. Eight studies were in that order. Ten of the women showed a greater cholesterol saturation and saturation index at PP than EB ($2p < 0{\cdot}02$). The saturation indices (mean $\pm$ SD) were: EB $0{\cdot}836 \pm 0{\cdot}204$; MC $0{\cdot}845 \pm 0{\cdot}183$; PP $0{\cdot}974 \pm 0{\cdot}220$. Relative concentrations of cholate, chenodeoxycholate and deoxycholate showed no significant trends. Fasting serum levels of cholesterol and triglyceride tended to be highest at mid-cycle, showing a significant fall 8-9 days later (cholesterol: $3{\cdot}84 \pm 0{\cdot}56$ and $3{\cdot}57 \pm 0{\cdot}53$ mmol/l, $2p < 0{\cdot}05$; triglyceride: $0{\cdot}65 \pm 0{\cdot}21$ and $0{\cdot}51 \pm 0{\cdot}13$ mmol/l, $2p < 0{\cdot}025$). These data suggest that in women of childbearing age, any tendency for gallstones to form will be greatest a few days before menstruation.

Duodenoscopic papillotomy and gallstone removal

P. B. COTTON, M. CHAPMAN, C. G. WHITESIDE, AND L. P. LEQUESNE (*Gastrointestinal Unit, Departments of Radiology and Surgical Studies, The Middlesex Hospital and Medical School, London, W1*) Using an experimental insulated Olympus duodenoscope and a diathermy wire, we have performed papillotomy on 10 sedated patients. Six patients had retained common bile duct stones following cholecystectomy; 3 of these still had T-tubes *in situ*, and cholate infusions had failed. One elderly patient had jaundice due to stones, and refused surgery. Three patients had papillary stenosis. Nine of the patients had severe medical or surgical contraindications to further operative management.

Papillotomy was successful in all patients, with no bleeding or other complication. Repeat endoscopy 1-2 weeks later demonstrated a bile duct orifice measuring 7-10 mm diameter. Stones had passed spontaneously in 3 of the 7 patients. In 2 others, they were extracted using balloon catheters or dormia type baskets. Two stones (10 and 11 mm diam) could not be removed, and in one of these patients, the stone and basket became impacted at the papilla and had to be removed surgically 2 days later. Follow-up on all the patients has been satisfactory, at 1-14 months. There has been no evidence of re-stenosis in the two patients examined again at 3 months, and one at 6 months.

Endoscopic papillotomy is a valuable new method for the removal of bile duct stones in high risk patients. If long term results are satisfactory, the technique will have wider application.

'Shock lung syndrome' in fulminant hepatic failure

P. N. TREWBY, RUTH WARREN, R. MACKENZIE, W. A. CROSBIE, J. LAWS, AND ROGER WILLIAMS (*The Liver Unit, Department of Radiology and Chest Unit, King's College Hospital, London, SE5*) Analysis of 100 consecutive patients with fulminant hepatic failure showed 37 to have clinical and radiological evidence of pulmonary oedema. Measurement of the pulmonary extravascular water volume confirmed the increased lung water (mean values 677 $\pm$ 117 ml in 4 patients with pulmonary oedema compared with 178 $\pm$ 19 ml in 8 controls, $P < 0{\cdot}001$).

Since cardiac involvement in fulminant hepatic failure is well described, left heart failure is one likely cause for the pulmonary oedema. However neither the right atrial pressure nor the heart size increased with the onset of oedema and in 12 patients the pulmonary artery wedge pressure was measured and found normal. These findings virtually exclude the presence of left heart failure and suggest the diagnosis of the shock lung syndrome.

There was no significantly increased incidence in the pulmonary oedema patients of endotoxaemia, infection, renal failure or hypoalbuminaemia; all postulated causes of shock lung, nor any correlation with cerebral oedema which is a frequent P.M. finding in these patients. Dexamethasone appeared of no prophylactic therapeutic value.

In many of these patients pulmonary oedema developed suddenly and unexpectedly and five deaths could be directly attributable to it. Awareness of the complication allows adequate ventilation and oxygenation and might reduce the risks of lung infection and secondary hypoxic brain damage.

Anomalous TSH secretion in liver disease; further evidence of hypothalamic-pituitary dysfunction

J. R. B. GREEN, E. J. SNITCHER, N. A. G. MOWAT, L. H. REES, R. P. EKINS*, AND A. M. DAWSON (*Departments of Gastroenterology and Chemical Pathology, St. Bartholomew's Hospital. *Department of Nuclear Medicine, Middlesex Hospital Medical School, London*) The diagnosis of thyroid dysfunction in patients with chronic liver disease often presents considerable problems. We have therefore studied 23 clinically euthyroid males with chronic liver disease and compared them with 27 normal male controls.

Patients had normal total serum thyroxine (T_4) but low total serum triiodothyronine (T_3), but when the free T_4 and free T_3 were measured they were normal, i.e. the clinical assessment of euthyroidism was confirmed biochemically. A binding protein abnormality is probably responsible for abnormal total T_3 serum concentrations.

Despite the normal circulating free hormone concentrations, basal thyrotrophin (TSH) concentrations were elevated. Since this may be an early feature of primary hypothyroidism, TSH release after thyrotrophin releasing hormone was investigated. Thirty-five per cent of patients had an abnormal delayed TSH response to TRH. This pattern of response is quite unlike that which occurs in latent primary hypothyroidism but has been described in patients with disordered hypothalamic-pituitary control of thyroid function. This is therefore a manifestation of more widespread hypothalamic-pituitary dysfunction in chronic liver disease as we have recently described other evidence of disordered hypothalamic-pituitary control of gonadotrophin secretion in the same patients[1].

The data show that extreme caution is required in interpreting thyroid function tests in chronic liver disease.

Reference

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The prognostic value of oesophageal investigations in patients with symptoms of gastro-oesophageal reflux

T. T. IRVIN AND C. PEREZ-AVILA (introduced by H. L. DUTHIE) (*The University Department of Surgery, The Royal Infirmary, Sheffield*) Various methods of investigation are used in the assessment of gastro-oesophageal reflux but the relative clinical and prognostic value of these investigations is uncertain.

The prognostic value of various oesophageal investigations was studied in 27 patients with symptoms of gastro-oesophageal reflux. The investigations included a barium meal, oral cholecystogram, upper alimentary endoscopy, acid perfusion[1] and acid clearing tests[2] oesophageal manometry, and overnight recordings of lower oesophageal pH. The patients then received medical treatment for their reflux symptoms and they were assessed after 4 months.

Eleven patients were completely relieved of their symptoms after treatment, 2 experienced partial relief, and 14 noticed no change. The response to treatment could not be predicted from the findings on the barium meal, oesophageal manometry and pH recordings. The acid clearing test had some prognostic value but the most useful investigations were the endoscopy and the acid perfusion test. Nine of the 10 patients with macroscopic oesophagitis at endoscopy were relieved of their symptoms, whereas only 2 of the 17 patients with a normal endoscopy experienced complete relief ($P < 0.001$). Eleven of the 16 patients with a positive acid perfusion test became symptom-free, and none of the patients with a negative test was relieved by treatment ($P < 0.001$).

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Relative value of clinical findings, early endoscopy, and multivariate analysis in patients bleeding from the upper gastrointestinal tract

A. G. MORGAN, W. A. F. MCADAM, G. R. WALMSLEY, JANE C. HORROCKS, AND F. T. DE DOMBAL (*Airedale General Hospital and the University of Leeds*) This study, involving 91 patients presenting to Airdale District General Hospital with haematemesis, had two aims. The first aim was an attempt to determine whether *multivariate analysis*, by combining individual patient attributes, enabled a prediction to be made of the short-term outcome from a patients clinical status on admission. Second, an assessment was made to determine whether addition of *endoscopic findings* conferred any predictive benefit—and hence to assess the value of early endoscopy in these patients.

Retrospective analysis of 40 patients confirmed that factors such as age, pre-existing disease and positive endoscopic findings carried a poor prognostic outlook. Subsequently, in a prospective series of 51 patients we combined these factors and studied their prognostic significance. When all three factors were combined, correct prognosis was possible in 70% of cases. When three further factors (alcohol, drugs, and heart failure) were added, the prognostic accuracy rose to 77%. Moreover, by formation of a simple prognostic rule, 16 of the 17 patients who re-bled were correctly identified. Finally, in a further test series, multivariate analysis proved more accurate than the prognostic 'estimates' of each of eight clinicians.

These results indicate that (i) multivariate analysis has some prognostic value in patients after haematemesis; and (ii) early endoscopy is valuable in increasing short-term prognostic accuracy.

The symptomatic significance of gastritis and endoscopic hyperaemia following gastric operations

A. M. HOARE, E. L. JONES, J. ALEXANDER-WILLIAMS, AND CLIFFORD HAWKINS (*Queen Elizabeth Hospital, Birmingham and General Hospital, Birmingham*) The relevance of endoscopic hyperaemia and gastritis seen after gastric operations is unknown as no controlled studies have been done[1]. In this paper 42 asymptomatic volunteer patients have been endoscoped and compared with matched patients with symptoms of dyspepsia and vomiting but no recurrent ulcer. Fourteen other patients had recurrent ulcers.

Histological gastritis was assessed using the criteria of Whitehead et al[2]. Some degree of gastritis was present in 89%, but was unrelated to symptoms. However, active fundal gastritis was commoner in symptomatic patients but this was not statistically significant. Atrophic gastritis did not occur in patients with recurrent ulcers.

Endoscopic hyperaemia correlated best with the type of operation and was found most commonly after partial gastrectomy and rarely after proximal gastric vagotomy. Severe hyperaemia was found in both symptomatic and asymptomatic patients. Erosions, oedema and contact bleeding occurred equally commonly in both groups. However, the combination of severe hyperaemia affecting most of the stomach and severe bile reflux with bile staining of the mucosa was found significantly more often in patients with dyspepsia and vomiting ($P < 0.05$).

The endoscopic appearance of mucosal hyperaemia is probably caused by bile reflux. This is commonly an incidental symptomless finding, but may cause discomfort and vomiting in certain patients.

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A prospective endoscopically controlled trial of double contrast against single contrast barium meals

M. I. LAVELLE, C. W. VENABLES, A. P. DOUGLAS, M. H. THOMPSON, J. P. OWEN, AND P. M. HACKING (*G.I. Group, Departments Radiology, Surgery and Medicine, Royal Victoria Infirmary, Newcastle upon Tyne*) Radiologists have suggested that double contrast (DC) barium meals are superior to single contrast (SC) (Kreel, 1973; Scott-Harden, 1973) but doubt exists on the best technique. This trial was designed to compare the 'Scott-Harden' technique with conventional radiology.

Two hundred and six patients were randomly allocated to DC (114) or SC examinations. Endoscopy was used as the definitive diagnostic procedure; all examinations being performed by experienced endoscopists within a maximum of 7 days of X-ray.

There was no difference between the techniques in diagnosing the presence of a DU (60% for both) and in false + ve diagnoses (DC 5/29: SC 5/16). Duodenal deformity was more accuratey diagnosed by DC (DC 98%: SC 74% $P < 0.01$).

Only 12 GUs were included in the trial but DC diagnosed 4/5 whilst SCfound only 3/7. Both methods were poor at defining 'normality' accurately (DC 43%: SC 38%). Chronic gastritis and peptic oesophagitis were rarely diagnosed by either technique.

In conclusion, this particular DC technique has advantages over SC but its accuracy is still unsatisfactory.

Deglycyrrhizinated liquorice in gastric ulcer: a double blind controlled study

K. D. BARDHAN, D. C. CUMBERLAND, R. A. DIXON, AND C. D. HOLDSWORTH (*Rotherham and Sheffield Hospitals and University of Sheffield*) Deglycyrrhizinated liquorice has been widely marketed over the last decade but its efficacy in the treatment of gastric ulcer remains undemonstrated in any large trial.[1]

In this double blind trial, 98 patients were randomly allocated to a 28-day regime of 2 capsules (450 mg) 5 times daily of deglycyrrhizinated liquorice (Ulcedal) or matched placebo. The groups were balanced for age and sex. After four weeks there was no significant difference between them in the proportion whose ulcers had healed.

However, there was little agreement between the radiological and gastroscopic assessments of ulcer healing. About 40% of patients showed healing, sometimes with gastritis, on gastroscopy, but on X-ray only about 25% had complete ulcer healing. About 50% were said to be healed by at least one of the two methods, but less than 15% by both methods.

All findings were confirmed by separate analyses: (i) of the 59 patients (29 on Ulcedal, 30 on placebo) who started with a gastroscopically confirmed single benign ulcer measuring more than 10 sq mm in maximum profile on X-ray, and (ii) of the remaining 39 patients (19 on Ulcedal, 20 on placebo) who had small or multiple ulcers or a recent haematemesis.

Reference

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Should peptic ulcer treatment relieve symptoms or heal ulcers?

M. H. THOMPSON AND C. W. VENABLES (*Department of Surgery, Newcastle University*) There is considerable discussion as to the desired outcome of treatment in peptic ulcer disease as between relief of symptoms and defined ulcer healing. Patients completing a 28-day double blind trial of metiamide versus placebo were asked to complete a self-rated assessment of their response, using a 100 mm line, before the final endoscopy, so the outcome of treatment was unknown at the time. Eleven patients were treated with metiamide and 10 with placebo: the mean scores were 83·2 and 82·3 respectively. ($P = 0{\cdot}72$). When the results were analysed in terms of ulcer healing, irrespective of treatment, the 'healed ulcer' group had a mean score of 93·3; 'unhealed ulcer' group a mean score of 71·1 ($P = 0{\cdot}029$). The ulcer healing, antacid consumption, and rate of loss of pain was not significantly different between the metiamide-placebo groups or the healed-unhealed groups. Furthermore, the 100 mm line test score correlated with other parameters of response such as antacid consumption in the metiamide treated group, but not in the placebo group.

It appears from these results that ulcer healing is the desirable outcome of treatment as far as patients themselves are concerned. Conventional parameters such as rate of loss of pain and antacid consumption may not always reflect the most desirable outcome.

Colonization of jejunum by enterobacteria and malabsorption in patients with giardiasis

A. M. TOMKINS, S. G. WRIGHT, B. S. DRASAR, AND W. P. T. JAMES (*Clinical Nutrition and Metabolism Unit, Department of Human Nutrition, London School of Hygiene and Tropical Medicine, Hospital for Tropical Diseases, London, and Bacterial Metabolism Research Laboratory, Colindale*) Malabsorption was present in 29 of 40 consecutively investigated young adults with giardiasis acquired in Africa, India and other parts of Asia. Twenty-three had impaired D-xylose absorption; in 20 vitamin B_{12} absorption was low and 15 patients had steatorrhoea. More severe malabsorption was associated with greater histological abnormality.

Nine out of 14 cases of giardiasis with severe malabsorption had high numbers of enterobacteria within mucosal and luminal samples of the upper jejunum. Four species of Enterobacteria (*Alcaligines faecalis, Enterobacter aerogenes, Enterobacter cloaca* and *Haffnia*) were isolated from 8 patients in numbers up to 10^7 $\log_{10}$ ml luminal fluid or g mucosa Enterobacteria were not present in 7 of 8 patients with mild malabsorption (xylose only) or in any of the patients without malabsorption.

Mucosal improvement occurred in 3 patients with severe malabsorption as *Giardia lamblia* and Enterobacteria were eliminated by a course of metronidazole therapy, but persistence of bacteria in a further two subjects despite eradication of *Giardia lamblia* was associated with a persistent mucosal lesion. Thus, the marked mucosal changes and malabsorption in our patients with giardiasis may reflect concomitant enterobacterial colonization rather than the effects of the parasite itself.

Lactulose-hydrogen (H_2) breath test in health and disease

G. METZ, D. J. A. JENKINS, AND L. M. BLENDIS (*MRC Gastroenterology Unit and Department of Gastroenterology, Central Middlesex Hospital, London, NW10 7NS*) Until recently there has been no satisfactory method of measuring mouth to caecum transit time. Now the hydrogen appearance time (HAT) in the breath after lactulose ingestion has been claimed as a simple and accurate method.[1]

We have measured HAT in 13 normal volunteers and 39 patients with various gastrointestinal disorders using a 33 g lactulose dose.

Mean HAT in controls was $85{\cdot}4 \pm 6{\cdot}7$ min. No controls had H_2 at 30 min. Of 15 patients being investigated for diarrhoea four had early HAT at 30 min or less and have been found to have hyperthyroidism(2), medullary thyroid tumour(1) and irritable bowel syndrome (IBS)(1). The remaining 11 diarrhoeal patients had normal transit and nine were eventually diagnosed as IBS.

Thirteen post gastric surgery patients were studied. Four were complaining of diarrhoea and two of these had early HAT. One Polya gastrectomy patient without diarrhoea had early HAT and was found to be colonised.

Of eight coeliac sprue patients three untreated cases with the most severe symptoms had a prolonged HAT of 150 min or longer. Two severely constipated patients had HAT of 90 min and 150 min and a third failed to produce H_2 by 4 hours.

In conclusion HAT after lactulose ingestion appears to be useful in investigation of abnormal bowel habit.

Reference

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Chronic diarrhoea and gluten sensitivity

B. T. COOPER, G. K. T. HOLMES, R. FERGUSON, R. THOMPSON, AND W. T. COOKE (*The Nutritional and Intestinal Unit, The General Hospital, Birmingham B4 6NH and Regional Immunology Laboratory, East Birmingham Hospital, Birmingham B9 5ST*) The characteristic diagnostic feature of coeliac disease is a 'flat' jejunal mucosa which improves towards normal on a gluten-free diet with remission of symptoms.

Nine women, aged 24 to 47 years, have been studied with a 6 month to 20 year history of diarrhoea, occurring both day and night, abdominal pains and distension, and lassitude. None had evidence of any gross gastrointestinal disease. Jejunal biopsies in all patients using a multiple biopsy capsule[1] on up to four separate occasions showed minor non-specific abnormalities with an increase in lamina propria plasma cell and interepithelial lymphocyte infiltration.

The patients were followed for 6 months to 7 years, during which time therapy, including a milk-free diet, was unsuccessful. In view of the continued troublesome symptoms, a gluten-free diet was started in each patient with striking clinical results. A jejunal biopsy while on the diet for at least 4 months showed a significant improvement in lamina propria and epithelial cellular infiltration.

A 30g gluten load was given to 8 patients following which symptoms were induced in 7, and a jejunal biopsy performed at 24 hours showed a significant fall in lamina propria lymphocytes in 7 patients. Plasma complement (Clq, C3, C4, C6, C7) levels for 24 hours after gluten challenge were relatively unhelpful.

On clinical and biopsy evidence, these patients are sensitive to gluten; therefore making a definition of coeliac disease even more difficult.

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Gluten antibodies (GA) in coeliac disease (CD) and dermatitis herpetiformis (DH)

B. B. SCOTT AND M. S. LOSOWSKY (*University Department of Medicine, St. James's Hospital, Leeds LS9 7TF*) GA titres are commonly raised in the serum of patients with CD, tending to fall on a gluten free diet. Less attention has been paid to these antibodies in DH. In one study[1] of DH, antibodies were not detected, possibly due to the frequently milder mucosal abnormality.

This study was designed to assess whether GA titres in CD are related to the degree of mucosal abnormality and, by analogy, whether differences in titres between CD and DH can be ascribed to differences in severity of the mucosal lesion.

Pre-treatment GA titres were all lower in CD patients with a convoluted mucosa than a flat mucosa. Twenty-two CD patients were matched with 22 DH patients for degree of mucosal abnormality, diet, and HL-A8. Milk antibodies (MA) were also measured as an index of the extent of mucosal abnormality[2]. GA titres were significantly higher in CD than DH ($P < 0.005$) but MA titres were similar. MA and GA correlated significantly for each condition but at any given levels of MA, the level of GA was much higher in CD than DH.

These findings suggest a fundamental difference in the immunological abnormality in CD and DH; possible explanations will be discussed.

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On the role of carbohydrate in gliadin toxicity in coeliac disease

FIONA M. STEVENS, J. J. PHELAN, B. MCNICHOLL, P. F. FOTTRELL, AND C. F. MCCARTHY (*Departments of Gastroenterology, Biochemistry and Paediatrics, Regional Hospital and University College, Galway*) The toxicity of wheat flour to patients with coeliac disease has been attributed to gluten and its ethanolic extract, gliadin. The persistence of gliadin toxicity after the action of common proteolytic enzymes together with the presence of carbohydrate on the gliadin molecules[1], suggested that the carbohydrate might be involved in the toxicity. Preliminary findings indicated that after the enzymic removal of carbohydrate the treated gliadin had no effect on D-xylose absorption in a coeliac patient[2].

Three coeliac patients who had been on gluten free diets were studied before and after being fed enzyme treated gliadin. The criteria for the assessment of toxicity were: D-xylose absorption, small intestinal morphology and brush border enzyme levels. In all three patients, gliadin toxicity was markedly reduced or abolished after the enzymic removal of carbohydrate. The chromatographic properties of the gliadin protein were unaltered by the treatment with enzymes.

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Farmer's lung and coeliac disease

T. J. ROBINSON (introduced by A. H. G. Love) (*Craigavon Area Hospital, N. Ireland*) There has been recent interest in the possible association of diffuse pulmonary disease and coeliac disease. Villous atrophy due to a gluten sensitive enteropathy has recently been described with extrinsic allergic alveolitis due to avian exposure (bird fancier's lung)[1]. A preliminary report suggests an association between farmer's lung and coeliac disease[2]. The present communication describes four cases in which the disorders coexist.

Two patients presented with acute dyspnoea and the classical features of farmer's lung confirmed by radiology and serology. They were noted to have features of malabsorption which in retrospect had been present for many years. The other two patients presented with steatorrhoea but had a past history of farmer's lung, one having chronic lung changes. All four had many features of malabsorption and on jejunal biopsy three showed a severe degree of villous atrophy. The fourth biopsy was reported as showing a normal villous pattern but there was increased cell infiltration. All responded clinically and symptomatically to a gluten-free diet.

It is suggested that coeliac disease should be considered in cases of farmer's lung and that the association between the two conditions requires further study.

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Immune complexes in ulcerative colitis—an experimental model

H. J. F. HODGSON, J. M. SKINNER, B. J. POTTER, AND D. P. JEWELL (*Department of Medicine, Royal Free Hospital, London, NW3 and Nuffield Department of Pathology, Radcliffe Infirmary, Oxford*) Evidence for the role of immune complexes in the pathogenesis of ulcerative colitis has been sought in an animal model, since some patients with the disease have immune complexes circulating in the blood[1] and show hypercatabolism of complement[2]. The model has been based on the Auer principle, that circulating complexes are deposited in sites of pre-existing inflammation.

Soluble immune complexes were made by precipitating human serum albumin (HSA) with anti-HSA at equivalence and redissolving the precipitate in excess HSA. One ml of 1% formalin was instilled into the rectum of rabbits; two hours later, the rabbits were given soluble complexes intravenously. Rectal biopsies were obtained at serial intervals. Control rabbits, given formalin, were injected with saline, antigen or antibody, alone.

Control rabbits showed minimal histological lesions which healed within 24 hours. Rabbits receiving immune complexes developed a severe inflammatory response within three hours, maximal at 7-8 days. The histological changes were those of severe ulcerative colitis. Three months later the mucosa had healed, the only abnormality being distorted glands.

These results suggest that once the rectum becomes mildly inflamed, the deposition of immune complexes either from the circulation or by local formation may result in a severe ulcerative disease.

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Enzymatic and quantitative histological evidence for Crohn's disease as a diffuse lesion of the gastrointestinal tract

W. T. DUNNE, ROBERT ALLAN, AND W. T. COOKE (*The University of Aston in Birmingham and the Nutritional and Intestinal Unit, General Hospital, Birmingham*) Previous work from this Unit suggests that Crohn's disease is a diffuse lesion of the gastrointestinal tract[1]. This study of enzymatic and quantitative histology extends this concept by identifying the microvilli as the site of abnormality. The aim of the investigation was to compare quantitative histological and enzymatic changes in the upper jejunum of patients with distal Crohn's disease, healthy controls and ulcerative colitis patients. Surface area, mucosal volume, brush border enzymes (measured by disaccharidase activity of three substrates) and cytoplasmic enzymes (measured by dipeptidase activity, of four substrates) were studied in jejunal biopsies from 20 patients with distal Crohn's disease, 14 with ulcerative colitis and 14 normal controls. In patients with Crohn's disease jejunal biopsy surface area was reduced and mucosal volume increased, with reduction in disaccharidase activity but no change in dipeptidase activity. These changes were related to neither disease activity nor its duration. No differences were obtained between ulcerative colitis patients and healthy controls. Reduction of brush border enzymes and normal cytoplasmic enzymes suggests specific damage to the microvilli and supports the concept of Crohn's disease as a diffuse lesion which might explain the high incidence of recurrent disease after surgical resection.

Reference

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Effect of azathioprine on cell-mediated immunity in Crohn's disease

J. M. T. WILLOUGHBY AND GILLIAN M. L. GYTE (*Departments of Medicine and Pathology, Lister Hospital, Stevenage, Herts.*) Two controlled trials have shown azathioprine to be of value in the short-term treatment of Crohn's disease[1,2]. Many clinicians, however, are deterred from prescribing longer courses of azathioprine by its designation as an 'immunosuppressive' compound, fearing that it will increase patients' susceptibility to malignant tumours by impairing their immune surveillance. This study employed one or more of three different tests in 34 patients with Crohn's disease to detect any suppression by azathioprine of their cell-mediated immune reactivity to *Candida albicans*.

The mean diameter of delayed skin reactions was lower in treated than in untreated patients, but 6 of 8 individuals re-tested after institution or withdrawal of azathioprine gave reactions differing negligibly from those first observed. Uptake of thymidine by lymphocytes incubated for five days with Candida was significantly greater in patients taking azathioprine than in those who had never received it ($P < 0.05$). No consistent effect of azathioprine treatment on leucocyte migration was discernible either in individuals or by group comparison.

Thus the only effect of azathioprine in these patients that could be reliably attributed to an action on the cell-mediated immune response was enhancement of in vitro lymphocyte reactivity. Further analysis revealed a clear relation between this and clinical improvement.

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Immune electron microscopy for viral particles in Crohn's disease

P. J. WHORWELL, R. C. BALDWIN, AND RALPH WRIGHT (*Professorial Medical Unit, Laboratory and Pathology Block, Southampton General Hospital, Southampton*) There have been recent reports of a transmissible agent in Crohn's disease[1] and a viral agent has been isolated by tissue culture techniques from this condition as well as in other gastrointestinal disorders[2]. We have therefore attempted to isolate and visualise viral particles from patients with Crohn's disease by electron microscopy. Operative specimens of diseased and control tissue were examined by direct and immune electron microscopy with negative staining after differential and density gradient centrifugation. Faecal specimens were studied in a similar manner.

No classifiable viral particles specific to the Crohn's disease tissue or stools were observed by either direct or immune electron microscopy. A small 12 nm particle of density 1·45 was found in abundance in all twelve of the Crohn's tissue specimens examined and in a small intestinal lymphoma. By contrast, after lengthy scanning, only very occasional

particles which appeared morphologically similar to those observed were seen in two of the controls but not in the remainder. The particles were not clumped by Crohn's or normal sera. The significance of these particles which are too small for any known virus, will be discussed.

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Induction of granuloma in CBA and A_2G strain mice by Crohn's disease tissue homogenates

D. R. CAVE, D. N. MITCHELL, AND B. N. BROOKE (*Surgical Unit, St. George's Hospital Medical School, London SW17*) Recent animal experiments suggest that Crohn's disease is a transmissible condition. Transmission experiments with the induction of granulomatous changes have been reported in CBA strain mice and New Zealand White rabbits[1,2,3]. This paper reports further experiments with normal and immunodeficient (T. 1000R) CBA strain mice and normal A_2G strain mice. Tissues were obtained from 9 patients with Crohn's disease and 5 control patients with diseases other than inflammatory bowel disease. Homogenized tissues either fresh or snap frozen were injected into the two hind footpads (0·03 ml) or the peritoneal cavity (0·5 ml) of the mice at 12 weeks of age. A total of 156 normal CBA, 60 immunodeficient CBA mice and 30 A_2G mice were used and each mouse received homogenate from one donor. Granulomatous changes were seen at footpad biopsy at 3 monthly intervals or at autopsy in the footpads, intestine, liver and/or spleen after Crohn's tissue injection but not after the injection of control homogenates. The granuloma inciting agent was present in Crohn's diseased ileum, colon, and mesenteric lymph node. Fresh, frozen, 100 μm and 0·2 μm filtrates of tissue homogenates all incited granulomas. Lesions were present in CBA and A_2G mice and evolved over 9 to 27 months after injection. These experiments provide further evidence that a transmissible agent is present in Crohn's disease tissues and that the agent is smaller than 0·2 μm.

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Antigen binding cells in rabbit Peyer's patches after intestinal immunisation

M. H. WANSBROUGH-JONES,* M. B. PEPYS, AND W. F. DOE (*Department of Medicine, Royal Postgraduate Medical School, Du Cane Road, London, W12 0HS*) Studies have been undertaken to investigate the induction of specific immunological responses to antigens administered via the intestine.

Rabbits were immunised by introducing sheep red blood cells (SRBC) on alternate days for 10 days into Thiry-Vella intestinal loops. The immunological response was assessed by counting the number of specific antigen binding (rosette-forming) lymphocytes in gut associated lymphoid tissues and the results are expressed as the number of rosette-forming cells per 10^6 lymphocytes ($\pm$ 1 SD).

A specific immunlogical response was detected in Peyer's patches in the fistulae (613 $\pm$ 194 compared with controls 79 $\pm$ 46, $P < 0.001$) and to a lesser extent in mesenteric lymph nodes (322 $\pm$ 53, controls 155 $\pm$ 70) in spleen (519 $\pm$ 215, controls 222 $\pm$ 72), and in Peyer's patches in the rest of the intestine (180 $\pm$ 60, controls 79 $\pm$ 46, $P < 0.02$).

After prolonged immunisation (SRBC alternate days for 16 doses) the response in the Peyer's patch of the fistulae was much enhanced (13,670 $\pm$ 2,104) but it could no longer be detected in lymphoid tissue elsewhere. Moreover, the response in the spleen to intravenously administered antigen was the same, whether or not antigen had been previously introduced into an intestinal loop (5,669 $\pm$ 2,212 and 10,503 $\pm$ 3,060 respectively).

Previous studies have failed to detect specific antibody production by Peyer's patch cells[1]. These results show that Peyer's patches can respond specifically to luminal antigen, and that extra-intestinal lymphoid tissue gives a primary response to intravenously administered antigen, whether or not the antigen has been previously applied on the intestinal mucosa.

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Studies on gastric D cell pathology

J. M. POLAK, S. R. BLOOM, M. MCCROSSAN, C. M. TIMSON, A. ARIMURA, AND A. G. E. PEARSE (*Departments of Histochemistry and Medicine, RPMS, London*) Since somatostatin is a local hormone controlling gastric acid secretion and gastrin release[1] it seems very important to study the morphology and relative distribution of the antral somatostatin producing D cells, previously identified by immunocytochemistry[2]. Unlike antral substance[3] producing cells the G cells and the somatostatin producing D cells are both localised in the mid-zone of the mucosa. Immunocytochemical staining for gastrin and somatostatin by the newly described serial semithin-thin section method[4] however, showed that the two hormones are definitely found in different cells.

The number of gastrin (G) and somatostatin (D) cells/unit area was compared in normal human antral biopsies. Quantitative immunocytochemistry revealed a preponderance of G over D cells (ratio 7:1). Abnormalities of somatostatin cells have been described previously only for pancreatic D cells[5]. We report here some preliminary findings on the D cells in the human antral mucosa.

Numerous antral biopsies were taken from three groups: (*a*) gastric ulcer (GU) with a subnormal number and distribution of G cells and an enormous relative increase in D cells (ratio 1:7); (*b*) duodenal ulcer (DU) with normal number and distribution of G cells (75% of all DU) also had normal D cell number (ratio 7:1); (*c*) DU with moderate to severe G cell hyperplasia (25% of all DU) had an absolute increase in immunostain intensity (optical density), hence hormone content, with a G/D ratio of at least 150:1.

Thus application of quantitative immunocytochemistry to the D and G cells (Automatic Image Analyser Computer) has given exciting new information on the pathophysiology of common diseases.

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Nitrite and thiocyanate in gastric juice

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Nitrosamines are powerful carcinogens in most animal species tested. Nitrosamine production by nitrosation of amines with nitrite can occur in human gastric juice[1]. Nitrosation is acid-dependent, catalysed by bacteria, and a thiocyanate concentration of 1 mmol/litre can accelerate nitrosation 550 times[2].

Exogenous amines and nitrite may be substrates for intragastric nitrosation and in this study the presence of endogenous nitrite and thiocyanate in the resting and secreting stomach has been examined.

In 17 patients having a standard pentagastrin test the mean basal nitrite concentration was 4·94 ± 1·13 (SE) μmol/litre. During stimulation the minimal nitrite concentration was 4·52 ± 1·01 μmol/litre and the maximal concentration was 5·76 ± 1·33 μmol/litre, neither of which were significantly different from the basal. In contrast the mean basal thiocyanate concentration fell significantly after stimulation from 0·96 ± 0·12 m mol/litre to 0·29 ± 0·04 mmol/ litre.

The mean basal nitrite concentration in smokers, 4·42 ± 1·63 μmol/litre, did not differ significantly from non-smokers, 5·16 ± 1·49 μmol/litre. In contrast the mean basal thiocyanate concentration in smokers, 1·12 ± 0·13 mmol/litre, was significantly higher than in non-smokers, 0·43 ± 0·12 mmol/litre.

The dilution of gastric juice thiocyanate during secretory stimulation suggests an extragastric origin such as saliva, and the difference between smokers and non-smokers could reflect salivary differences[3]. In contrast the maintenance of nitrite concentration during secretion suggests the possibility of a gastric origin, and active secretion of nitrite by the stomach cannot be excluded. The presence of nitrite and thiocyanate in fasting and secreting stomachs may have potential carcinogenic significance.

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Gastric mucosal permeability—a relationship between ischaemia and cellular damage

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Many factors have been implicated in the aetiology of gastric ulceration. This work describes a direct link between transient mucosal ischaemia, altered permeability and cellular damage.

PERMEABILITY STUDIES

To investigate this association a small disposable chamber has been used to measure *in vivo* the permeability of the gastric mucosa to the tracer technetium^{99}.[1] Control experiments in 20 anaesthetized rabbits placing 0·25 mc ^{99}Tc on the mucosa of chambered segments of either antrum or fundus and measuring activity in femoral venous blood demonstrated a greater permeability in the antral areas when compared with the fundus (1·46:1). A similar ratio of blood flow to these areas has been demonstrated by the indicator fractionation technique of Saperstein using $Rb^{86}Cl$.[2]

BLOOD FLOW STUDIES

Mucosal ischaemia was induced by the infusion of 1 unit of vasopressin every 5 minutes for 15 minutes. Simultaneous BP recordings were made with an intra-arterial cannula connected to a Minograph recorder. From chambered segments of fundic mucosa the uptake of tracer was halted during the infusion. Fifteen minutes after stopping the infusion, however, the permeability of the fundic mucosa increased significantly above control values. Experiments in antral areas demonstrated no associated increase in permeability after ischaemia.

HISTOPATHOLOGICAL STUDY

Tissue from antral and fundic areas was examined by light and electron microscopy taken (1) before vasopressin, (2) during ischaemia, (3) during the phase of increased permeability. At light microscopy there was no detectable change in any phase. Electron microscopy, however, revealed intracellular lesions, particularly of the mitochondria with clumping of nuclear chromatin, which was evident in the fundic mucosa at the time of increased permeability—the antrum being spared.

The triad of transient mucosal ischaemia, increased permeability and organelle damage may be of significance in considering the aetiology of gastric ulceration.

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The study of the gastric mucopolysaccharides of patients with duodenal ulceration and X-ray negative dyspepsia by discriminant function analysis

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It has been shown previously, with 96·8% accuracy, that it was possible to distinguish between a group of 42 patients with confirmed duodenal ulceration and a group of 22 normal volunteers by using a multiple discriminant function analysis on the products of mucopolysaccharide secretion of the gastric juice obtained during a pentagastrin stimulation test[1].

Confirmation of these results has now been obtained by studying a further group of 18 patients whose diagnoses were unknown to the investigators. Fourteen cases were correctly allocated, 1 was wrongly classified and 3 were of doubtful status when a sub-set of the original 20 variables were compared with the original two groups.

This work has been extended to cover a further 27 patients with proven duodenal ulceration, 17 with X-ray negative dyspepsia and the 22 controls. It has been clearly shown that the study of the sugar and nitrogen constituents of the gastric juice enabled the separation of the normal controls from both the duodenal ulcer group and the dyspeptic group with

statistically significant results. A degree of variation was obtained between the two groups of patients but it was not significantly different.

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Distribution of 5-FU to body tissues compared after intravenous, intraluminal and intramural administration in gastrointestinal cancer

H. S. SHUKLA, P. W. DAVIS, K. G. LEACH, AND L. E. HUGHES (*University Department of Surgery, Welsh National School of Medicine and the Department of Medical Physics, The University Hospital of Wales*) Poor survival from gastrointestinal cancer has led to trials of different types of adjuvant therapy. 5-Fluorouracil administered intraluminally during the resection of colorectal cancer has been reported to increase the survival in Dukes' 'C' cases[1]. This is believed to be due to preferential distribution in the lymphatics and portal bloodstream, a hypothesis which has not been tested in the clinical situation.

We have investigated distribution of 5-FU in various body tissues following administration by each of three routes—intravenous, intraluminal and intramural.

Labelled 5-FU (^{3}H or ^{14}C) was administered by one of these routes to 32 patients at surgery for gastric or colonic cancer. Samples were taken of systemic venous blood, portal venous blood, tumour, normal bowel, draining lymph node, liver and skin. Radioactivity was measured by liquid scintillation counting and expressed as 5-FU per g of tissue, and as a percentage of the total dose administered.

5-FU levels were considerably higher (by a factor of approximately 12) when given by the intramural route, in lymph nodes, portal blood and liver. This work suggests that a clinical trial of intramural adjuvant chemotherapy is indicated, and might be expected to give better results than those reported with the intraluminal route.

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