Gut, 1975, **16**, 821-845

The British Society of Gastroenterology

The 36th annual meeting was held in Oxford on 25–27 September under the Presidency of Dr S. C. Truelove. The meeting proper was preceded by a teaching day on 24 September when there were two sessions, one on liver disease (Chairman: Dr J. Badenoch), and the other on gastrointestinal disorders (Chairman: Sir Francis Avery Jones). There were 14 sessions each allocated to a different subject, and in addition there was a plenary session and panel discussion on 'The management of ulcerative colitis'. The Sir Arthur Hurst Memorial Lecture, 'Towards an artificial liver', was given on this occasion by Dr Roger Williams. Abstracts of the scientific papers follow and a more general report of the meeting and of the social events can be found on page 846.

Distribution of gut hormones

S. R. BLOOM, M. G. BRYANT, AND J. M. POLAK (*Departments of Medicine and Histochemistry, The Royal Postgraduate Medical School, Hammersmith Hospital, London*) Although several new gut hormones have recently been described there is little precise information on their site of origin.

Four adult baboons and three monkeys which had been maintained on human diet for a number of years were studied. The gastrointestinal tracts were removed from the freshly slaughtered animals, rapidly divided into nine anatomical regions and plunged into freezing acid ethanol. The hormones were solubilized by three separate tissue homogenizations and solid material was removed by centrifugation. The supernatants were then neutralized, dried down and redissolved on buffer for radioimmunoassay.

In the baboons the greatest amount of gastrin was found in the antrum (10 ± 1 (SE) μg) and duodenum (5·1 ± 0·3) and pancreatic glucagon in the gastric fundus (1·1 ± 0·03 μg) and pancreas (259 ± 32 μg). Enteroglucagon was greatest in the ileum (66 ± μg) but significant amounts were also found in the colon (40 ± 19 μg). Secretin was greatest in the duodenum (3·6 ± 0·3 μg) and jejunum (6·9 ± 1·2 μg) and gastrointestinal peptide (29 ± 4 μg) and motilin (31 ± 3 μg) in the jejunum. Vasoactive intestinal peptide was present in largest amount in the colon (235 ± 84 μg) and ileum (105 ± 23 μg) but significant quantities were present in the fundus (24 ± 2·5 μg), duodenum (12 ±3 μg) and jejunum (28 ± 5 μg). The concentration per gram gut was very similar in the monkeys though some variation in total amount was seen due to different organ weights. Immunocytochemical data on hormone distribution were in substantial agreement.

These hormone maps provide baseline data for physiological studies.

Bile acid-mediated absorption in the ileum of a patient with congenital chloridorrhoea

J. RASK-MADSEN, J. KAMPER, AND E. KRAG (*Medical Departments F and B, Glostrup and Gentofte University Hospitals, Copenhagen, Denmark*) In an 8-month-old child with congenital chloridorrhoea bidirectional fluxes of Na, K, and Cl, and net transfer of water and HCO_3 were measured simultaneously with the transmural potential difference (pd) during steady state perfusion of the intestine. In ileum, water, Na, K and Cl were secreted, and HCO_3 was absorbed from isotonic perfusates. The lumen side was 95[3] mV negative to blood. Only Cl was transported against both electrical and chemical gradients but discrepancies between observed and predicted flux ratios indicated that a Na-absorbing mechanism was active as well. Tracer fluxes showed that the epithelium was impermeable to Cl in the direction lumen plasma. In the presence of 2·5 mMol glycochenodeoxycholic acid, Na and water were absorbed, while net transfer of Cl was abolished. No significant changes in pd, luminal pH or pCO_2 could be demonstrated. In jejunum, water and electrolyte transport was normal, and the PD −3 mV. The abnormal transport in ileum can be explained by the model of Schultz and colleagues[1] if an inversion of the brush border transport processes is postulated. Since only the neutral NaCl influx mechanism is inhibited by cAMP, this model also satisfies the paradoxical effect of bile acids in congenital chloridorrhoea. Subsequently, a clinical trial was done. Following oral administration of coated theophylline the frequency and the volume of the diarrhoeas decreased significantly.

Reference

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Investigation and treatment of a recurrent vipoma

J. R. LENNON, W. SIRCUS, S. R. BLOOM, S. J. MITCHELL, J. M. POLAK, G. M. BESSER, R. HALL, D. H. COY, A. J. KASTIN, AND A. V. SCHALLY (*The Gastrointestinal Unit, Western General Hospital, Edinburgh, and Departments of Medicine and Histochemistry, The Royal Postgraduate Medical School, Hammersmith Hospital, London*) Vasoactive intestinal peptide (VIP) has been extensively studied in a case of the Verner-Morrison syndrome[1]. The patient developed severe electrolyte-depleting diarrhoea in 1967 which promptly disappeared after removal of a pancreatic islet cell tumour[2,3]. Diarrhoea recurred with hepatic metastases showing VIP immunofluorescence in August 1974. The plasma VIP concentrations, measured by radioimmunoassay, were 300-400 pg/ml (n < 50). The diarrhoea stopped with prednisolone therapy and VIP fell to less than 150 pg/ml. On temporary withdrawal of steroids diarrhoea returned and the VIP rose concomitantly. Following three months of steroid control diarrhoea appeared again and break-

through of VIP release was found, the levels rising to over 600 pg/ml.

The volume of fluid aspirated from the distal duodenum was reduced from a mean of 8·7 ± 0·9 (SE) ml/10 min in the basal hour to 3·7 ± 0·7 ml/10 min during an 80-minute intravenous infusion of 750 μg of somatostatin, with a rebound rise to 16·3 ± 2·5 ml/10 min in the hour following infusion. Vasoactive intestinal peptide levels fell rapidly during infusion from 800 pg/ml to 550 pg/ml with a rebound to 950 pg/ml following. Vasoactive intestinal peptide was unaffected by meals, intravenous secretin and iv calcium.

Three intrahepatic artery infusions of streptozotocin have stopped all diarrhoea, though profuse watery stools occurred in the hour after each infusion. The effect of streptozotocin on plasma levels of VIP and gastrin will be reported.

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Inhibition of enterotoxin-induced intestinal secretion by the polypeptide antibiotic, Polymyxin

J. G. BANWELL, H. N. MAIMON, AND DAN HANKE (*Gastroenterology Division, University of Kentucky Medical School, Lexington, Kentucky, USA*)

The copious diarrhoeal fluid loss of cholera is a result of interaction of cholera enterotoxin (CT) with the intestinal mucosa. Fluid secretion is dependent on binding of CT to specific mucosal receptors (ganglioside GM_1) and activation of membrane-bound adenylate cyclase. This process may be susceptible to inhibitions by agents which preferentially bind to the mucosal surface. Polymyxin sulphate (1 mM), an antibiotic which binds to phospholipids of cell membranes, reduced net fluid secretion 96% in isolated and perfused rabbit intestinal loops exposed to cholera enterotoxin. Binding of ^{3}H-Polymyxin to isolated brush border membranes was temperature dependent and competitively inhibited by free Polymyxin. No histological damage or alteration in brush border disaccharidase activity was detected in mucosa exposed to Polymyxin under these conditions. Polymyxin inhibited the fluid secretory response to *E. coli* enterotoxin, as well as to CT. Activation of mucosal adenylate cyclase by CT was partially inhibited by pretreatment with Polymyxin. Polymyxin or similar agents, which act on the intestinal mucosal cell surface, may have a therapeutic role in control of enterotoxin-induced diarrhoeal fluid loss.

Jejunal biopsy in the management of infants suspected of cow's milk protein intolerance

MARGOT SHINER, JANET BALLARD, C. G. D. BROOK, S. HERMAN, AND D. LOVELL (*Medical Research Council Gastroenterology Unit and Department of Paediatrics, Central Middlesex Hospital, London*)

Cow's milk protein intolerance in infancy remains a controversial entity, since the clinical reaction of infants suspected of sensitivity to cow's milk is variable.

We have attempted to put the diagnosis on an objective basis by taking patients suspected of cow's milk protein intolerance off cow's milk, substituting a hydrolysed casein or soya bean formula, and by following this elimination diet by cow's milk challenge studies several weeks later.

Before the challenge lactose intolerance was excluded and the following examinations were carried out: (1) eosinophil counts, (2) serum immunoglobulins and IgE antibodies specific to cow's milk, and (3) jejunal biopsy. These were repeated between six and 28 hours after challenge with 5-20 ml of cow's milk. All jejunal biopsies were examined histologically, ultrastructurally and by immunofluorescent techniques.

Five patients with histories suggestive of cow's milk protein intolerance will be presented. In three it was not possible either clinically or from the examination of blood or stools to predict the findings on the postchallenge biopsy specimen. In affected individuals the postchallenge mucosa showed blunting of the jejunal villi, dense mucosal inflammation, mast cell degranulation, oedema, collagen deposition and endothelial hypertrophy. Immunologically there was evidence of an early reaginic and a late Arthus reaction.

Since no other test is diagnostic of cow's milk protein intolerance we regard jejunal biopsy before and after cow's milk challenge as essential in the management of children suspected of this condition.

Inhibition of aspirin and taurocholic acid-induced gastric mucosal bleeding by prostaglandin 15(R)15 methyl-E2 methyl ester

H. A. CARMICHAEL, L. NELSON, V. CHANDRA, A. LYON, K. M. COCHRAN, AND R. I. RUSSELL (*Gastroenterology Unit, Royal Infirmary, Glasgow*)

It has been shown that conjugated bile acids, in particular taurocholic acid, significantly increase the incidence of aspirin-induced gastric mucosal erosions in rats.[1] Prostaglandins have been shown to inhibit the production of stress-induced and indomethacin-induced gastric ulceration in rats.[2]

We have investigated the effect of prostaglandin 15(R)15 methyl E2 methyl ester on taurocholic acid and aspirin-induced gastric mucosal bleeding in rats.

Aspirin (64 mg/kg) and taurocholic acid (2·5 mM) (solution adjusted to pH 4·5) caused mucosal bleeding in 53·6% of rats. The addition of prostaglandin (50 μg/kg) under control conditions significantly reduced the incidence of bleeding to 19·5% ($P < 0.01$). Aspirin alone (128 mg/kg) caused bleeding in 80% of rats: this incidence was significantly reduced to 20% by adding prostaglandin (50 μg/kg) ($P < 0.002$). No significant bleeding was induced by increasing concentrations of taurocholic acid alone (up to 20 mM).

This prostaglandin analogue may prove to be of value in the prevention and possibly the treatment of aspirin-induced gastric pathology.

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The effect of sodium taurocholate on the permeability of antral and fundic gastric mucosa

D. H. BIRKETT AND I. MCCOLL (*Department of Surgery, Guy's Hospital, London*)

Sodium taurocholate increases the physical permeability of fundic gastric mucosa[1], but its effect on permeability

of antral mucosa is unknown. *In vitro* rabbit antral and fundic gastric mucosa, mounted in Ussing chambers, were perfused with an oxygenated bicarbonate solution. 20 mM taurocholate at pH 7·4 or 2 mM taurocholate at pH 2·5 were added to the mucosal solution for two hours in 10 experiments each, all with controls. Transmucosal flux of erythritol-C^{14}, and tissue resistance were used to measure alterations in mucosal permeability. After two hours, taurocholate at pH 7·4 increased erythritol flux across antral mucosa compared with controls, 3·19 ± 0·48 and 1·20 ± 0·27 picomoles/cm²/sec respectively ($P < 0·005$), and reduced resistance, 92·02 ± 7·34 compared with 158·11 ± 11·77 ohms. cm² ($P < 0·001$). In fundic mucosa taurocholate failed to increase flux, 2·89 ± 0·45 compared with 2·07 ± 0·45 picomoles/cm²/sec ($P < 0·05$), but did significantly reduce resistance, 121·72 ± 8·62 compared with 161·15 ± 6·41 ohms. cm² ($P < 0·005$). At pH 2·5 taurocholate increased erythritol flux across antral mucosa, 13·97 ± 5·15 compared with 1·37 ± 0·34 picomoles/cm²/sec ($P < 0·001$), and reduced resistance, 43·56 ± 12·16 compared with 189·53 ± 11·26 ohms. cm² ($P < 0·001$). In fundic mucosa taurocholate increased flux, 5·73 ± 1·03 compared with 0·82 ± 0·15 picomoles/cm²/sec ($P < 0·001$), and reduced resistance, 81·05 ± 7·80 compared with 198·32 ± 9·93 ohms. cm² ($P < 0·001$). In treated mucosa the slope of the regression of flux against time was significantly greater in antrum than fundus indicating greater antral permeability. At both high and low pH the increase in physical permeability caused by taurocholate is greater than antral than in fundic mucosa. This greater increase of permeability in antral mucosa may be a reason for the site of gastric ulcer formation.

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The relationship between antro-fundic permeability and gastric mucosal blood flow using tracer techniques

B. M. NEWMAN, T. V. TAYLOR, J. B. ELDER, AND I. E. GILLESPIE (*University Department of Surgery, Royal Infirmary, Manchester*) The relationship between gastric mucosal permeability and gastric mucosal blood flow remains obscure. Others[1] have reported differences in permeability between antrum and fundus but no adequate explanation has been forthcoming.

PERMEABILITY STUDIES

To investigate this problem a small disposable chamber has been used to measure *in vivo* the permeability of gastric mucosa to the tracer Technetium^{99}. Control experiments in 20 anaesthetized rabbits placing 0·25 mc of Technetium^{99} on the mucosa of chambered segments of either antrum or fundus, and measuring activity in venous blood, demonstrated significantly greater permeability in the antral areas as compared with the fundus ($P < 0·005$). The ratio in permeability to Technetium of antrum : fundus was 1·46:1.

BLOOD FLOW STUDIES

Using the indicator fractionation technique of Saperstein[3] with Rubidium^{86} in rabbits and rats, the gastric mucosal blood flow in the antrum was found to be uniformly greater than in the fundus. Blood flow ratio of antrum : fundus was 1·5:1 using rabbits and 1·4:1 using rats in the fasting state.

There appears to be a close correlation of the ratios for antro-fundic permeability and for antro-fundic blood flow under the conditions of study.

The similarity of the ratios for antro-fundic mucosal blood flow to the ratio for antro-fundic permeability to ^{99m}Tc is striking and suggests that the two phenomena are related, the antrum having a significantly greater mucosal blood flow and permeability.

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Inhibition of glucosamine synthetase by ulcerogenic and non-ulcerogenic drugs

M. J. GOODMAN, P. W. KENT, AND S. C. TRUELOVE (*Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford*) It has been postulated that peptic ulceration induced by the anti-inflammatory drugs is due to the inhibition of gastric mucus production. In particular, it has been shown in rat gastric mucosa that salicylates inhibit the enzyme glucosamine synthetase (L-glutamine-D-fructose-6-phosphate aminotransferase) which is probably a rate-limiting step in mucus biosynthesis[1].

In reports in the literature, the ulcerogenic drugs have been compared with control systems in which the particular drug was omitted but it has been unusual to compare them with non-ulcerogenic drugs. We have studied the inhibition of glucosamine synthetase *in vitro* in homogenates of human gastric and colonic mucosa by aspirin, sodium salicylate, hydrocortisone and paracetamol. Hydrocortisone was rather more inhibitory than the other drugs, but aspirin, sodium salicylate and paracetamol were inhibitory to a similar degree, with 50% inhibition occurring at 23, 27 and 29 mM respectively. Gentamicin also inhibited the enzyme by about 50% at 22 mM. Hence the inhibition of glucosamine synthetase by the ulcerogenic drugs is a non-specific effect which is also shown by non-ulcerogenic drugs. Studies of the mechanism of drug-induced peptic ulceration should include comparisons with non-ulcerogenic drugs.

Reference

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Effect of a pepsin-inhibitory pentapeptide upon the gastric secretion of pepsin and hydrochloric acid

P. M. CHRISTIANSEN, L. B. SVENDSEN, N. GULDAGER, AND L. CHRISTENSEN (*University Department of Surgical Gastroenterology, Bispebjerg Hospital, Copenhagen*) A pentapeptide, pepstatin, has been developed in Japan[1]. The effect of this pentapeptide upon the gastric production of pepsin and hydrochloric acid was investigated in nine men with ulcer dyspepsia and a high acid output. Subtotal inhibition of peptic activity was obtained, basally as well as after broth stimulation, as early as 15 minutes after the administration, and the inhibition remained almost unchanged during the 60 minutes of the experimental period. Acid secretion was not affected by pepstatin. No side effects occurred. The results confirm Japanese reports on the pepsin-inhibitory activity of the drug[1,2]. It is concluded that pepstatin ought to be investigated with regard to its clinical effect upon peptic ulcer.

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Mucosal flora of the human colon

S. L. PEACH, B. S. DRASAR, P. R. HAWLEY, M. J. HILL, AND C. G. MARKS (*Bacterial Metabolism Research Laboratory, Colindale, London, and St Mark's Hospital, London*) Studies of animals have suggested a specific mucosal-dependent flora in the colon (Savage, 1972). Studies of human colonic mucosa have been limited because of the difficulties of obtaining material under suitable conditions.

Specimens of colonic mucosa and tumour were taken at the time of operation from patients undergoing large bowel surgery. A stool specimen was taken simultaneously in order to examine the interrelationship between the flora of mucosa, tumour and faeces.

Mucosal and tumour flora were similar but differed quantitatively from the faecal flora. Unlike the faeces, the mucosal flora was not dominated by anaerobic bacteria. Whereas in the lumen of the large bowel anaerobic bacteria outnumber aerobic bacteria by 100:1, this ratio is close to unity from mucosal specimens.

Preoperative treatment with phthalylsulphathiazole was not associated with any marked change in the number and types of bacteria isolated from mucosa and tumour specimens. This is in contrast to the effect of antibacterial agents on the faecal flora, which have been described and may have wider implications with regard to studies of preoperative bowel preparation.

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Prophylactic oral antimicrobial agents in elective colon surgery: A prospective controlled clinical trial

J. GOLDRING, A. SCOTT, W. MCNAUGHT, AND G. GILLESPIE (*Departments of Surgery and Bacteriology, Victoria Infirmary, Glasgow*) Attempts to reduce the infective complications of colonic surgery by the use of prophylactic antibacterial agents have provoked much controversy but few adequately conducted clinical trials (Cohn, 1970). In particular, little attempt has been made to control anaerobic bacteria, the predominant group of faecal organisms and recently the subject of revived interest (Leigh, 1975).

In a controlled clinical trial a combination of kanamycin and metronidazole was chosen to take account of both aerobic and anaerobic bowel organisms, and administered orally preoperatively to 25 patients undergoing elective colon surgery with a similar group acting as controls. A highly significant reduction in the number of coliforms ($\chi^2 = 21{\cdot}01$; $P < 0{\cdot}00025$) and bacteroides ($\chi^2 = 23{\cdot}45$; $P < 0{\cdot}00025$) was observed in the colons of the study group, in addition to a significant reduction in wound sepsis ($\chi^2 = 6{\cdot}65$; $P < 0{\cdot}01$). No complications attributable to these drugs were encountered. No single agent presently available offers control over the total colonic microflora. The combination of kanamycin and metronidazole fulfils the three major requirements for an effective intestinal antiseptic (Cohn, 1958) and was both safe and effective in the present trial.

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Antibiotic-induced pseudo-membranous colitis

C. E. CLARK, S. J. A. POWIS, A. R. CRAPP, M. R. B. KEIGHLEY, AND J. ALEXANDER-WILLIAMS (*The General Hospital, Birmingham*) Lincomycin-induced pseudomembranous colitis is a recognized clinical entity, but the pathogenesis is ill understood and probably multifactorial[1]. Nevertheless lincomycin is an extremely efficient antibiotic in reducing the incidence of bacteroides infection after bowel surgery[2]. In a recently conducted prospective controlled randomized trial to study the incidence of wound infection after large bowel surgery, 33 patients received 600 mg lincomycin eight hourly for five days and no case of pseudomembranous colitis was seen.

Subsequently lincomycin has been combined with a broad-spectrum antibiotic (gentamicin or tobramycin) and given prophylactically for a shorter period, to cover the operation and first postoperative day. Of 18 patients so treated, six have developed pseudomembranous colitis, and of these one has died.

We also have knowledge of two patients who have received lincomycin and a broad-spectrum antibiotic given for therapeutic reasons, who developed pseudo-membranous colitis and of these one died.

This experience is contrary to that of Stokes *et al*[3] who combined lincomycin and gentamicin therapy in 97 patients without a case of colitis being seen.

It would seem that a short course of lincomycin does not prevent this serious complication, particularly when combined with a broad-spectrum antibiotic.

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Colon cancer and bacterial metabolism in familial polyposis

B. S. DRASAR, E. S. BONE, M. J. HILL, AND C. G. MARKS (*Bacterial Metabolism Research Laboratory, Colindale, London, and St. Mark's Hospital, London*) In a previous study of patients with cancer of the large bowel we demonstrated that the faeces of 70% of these patients contained the combination of a high concentration of bile acids and carried clostridia able to dehydrogenate the steroid nucleus. This contrasted with a similar hospital population without large bowel cancer, of whom only 9% produced this combination of results on faecal analysis[1].

To evaluate the significance of these findings a large group of normal people and various groups of patients with a high risk of developing bowel cancer are being studied on a prospective basis. One such group are the relatives of patients with familial polyposis, who, if they develop polyposis, will usually go on to develop cancer. Patients who had developed polyps and as yet unaffected subjects were studied[2].

None of the subjects who had already developed polyps and only a small proportion of the others had this combination, thus our postulated environmental factor cannot explain the high risk of large bowel cancer in this population. Indeed, as a group these patients were remarkable for the lack of activity of

their intestinal bacteria. There is no obvious explanation for these findings. When examined *in vitro* the faecal flora was not apparently abnormal. Intestinal transit was normal and thus ample time for bacterial action is available.

Nevertheless in those who developed polyps the gut bacteria failed to degrade cholesterol or to produce the cyclic secondary amines usually excreted in the urine; the faecal bile acids were also largely intact. This pattern of bacterial inactivity was also found in about half of the unaffected siblings. Further studies are in progress to determine the success of these findings in predicting those siblings who will develop polyps.

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Differential colonic transit time and the relationship between intraluminal pressure and transit in the colon

W. O. KIRWAN AND A. N. SMITH (*Department of Clinical Surgery and Wolfson Gastro-Intestinal Laboratories, Western General Hospital, and University of Edinburgh*) An isotope capsule[1,2] has been used to study differential colonic transit time in diverticular disease, constipation and the irritable colon syndrome. It is possible, using this method, to determine the transit time for various colonic segments and to demonstrate areas in which delay occurs. Colonic transit time can be abnormally long in all these conditions. Delay may occur in the rectosigmoid (29 $\pm$ 4 hours before bran and 18 $\pm$ 2 hours after bran, $P < 0.0025$), in the region of the splenic flexure (26 $\pm$ 2 hours before bran and 16 $\pm$ 2 hours after bran, $P < 0.0005$), in the transverse colon (24 $\pm$ 0 hours before bran and 16 $\pm$ 2 hours after bran, $P < 0.0025$) and in the right colon (25 $\pm$ 5 hours before bran; 16 $\pm$ 2 hours after bran, $P < 0.0025$). Delay therefore occurs throughout the entire colon, and bran exerts an effect on transit throughout its length.

The relationship between transit time and colonic intraluminal pressure was found, surprisingly, to be an inverse one ($m = -0.14, -0.22, -0.38$, $P < 0.05$) for basal, postfood and postprostigmine phases of motility recording. It is concluded that segmenting colonic contractions serve to advance the intraluminal contents.

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Colonic pseudo-obstruction complicating jejuno-ileal bypass: The role of intestinal flora

R. E. BARRY, A. W. CHOW, J. BILLESDON, J. R. BENFIELD, AND S. L. GORBACH (*UCLA School of Medicine and Harbor General Hospital, California*) (introduced by A. E. Read, *University of Bristol, Department of Medicine, Bristol Royal Infirmary*) We have observed eight cases of colonic pseudo-obstruction as a late (> one yr) complication of jejuno-ileal bypass. The pathogenic role of intestinal flora has been examined (five patients) in a random-sequence, double-blind cross-over study using antiobiotics chosen specifically to delineate the relative roles of aerobic and anaerobic organisms. Quantitative bacterial cultures were obtained before and after each antibiotic course from the bowel immediately proximal and distal to the site of drainage of the blind loop. Samples were transported in gassed vials and processed according to VPI technique. Metronidazole produced 31/33 pain-free days compared with 0/33 before treatment and consistently decreased abdominal girth (mean -2.9 cm). Clinical improvement was associated with a fall in the anaerobic population in the vicinity of the blind loop from a mean of 8·9 logs/ml before treatment to 0·9 logs/ml after treatment. Placebo produced only 9/34 pain-free days and mean girth increased $+3$ cm. This deterioration was associated with return of anaerobes (mean 1·5 logs/ml rising to 6·25 logs/ml). Kanamycin produced only 14/33 pain-free days, girth and bacterial counts remaining virtually unchanged. The combination of metronidazole + kanamycin produced similar results to metronidazole alone.

It is concluded that symptoms of pseudo-obstruction are related to bacterial flora in proximity to the defunctioned bowel. Obligate anaerobes play a more decisive role.

Coeliac disease: A new aetiological hypothesis and possibly a new treatment

ADRIAN P. DOUGLAS (*Gastroenterology Group, Department of Medicine, Royal Victoria Infirmary, Newcastle upon Tyne*) Many of the features of the effect of wheat gluten on coeliac intestinal mucosa suggest that the protein is acting as a lectin and that its toxicity is analogous to that of concanavalin A on tumour cells[1]. Such a hypothesis would suggest that coeliac mucosal cells have an abnormal, or normally cryptic, receptor site on their plasma membrane.

With these concepts in mind a glycoprotein material (Glyc-glu) has been extracted from wheat gluten. This contains 10·3 μg sialic acid/mg protein, 25·7 μg hexose/mg protein and included amongst these hexoses are fucose, mannose and rhamnose. Its amino acid composition is uniquely different from gluten and α-gliadin. It is toxic to treated coeliac mucosa when fed in small quantities (0·5 g/day) and it is capable of binding to intestinal mucosa using an assay system with iodinated I^{125}-Glyc-glu. This binding occurs only slightly with normal intestinal mucosa and has characteristics similar to the affinity for cell membranes described for other lectins. The binding can be prevented by the presence in the incubation mixture of certain simple sugars including arabinose and rhamnose. Similar studies with iodinated α-gliadin show that this protein does not bind to coeliac mucosa in appreciable amounts.

These observations provide a new explanation for the mechanism of gluten toxicity in coeliac disease and suggest that simple sugars by behaving as sugar haptenes may provide a new approach to treatment.

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Bird fancier's lung and coeliac disease

W. T. BERRILL, O. E. EADE, W. M. MACLEOD, I. G. GARDINER, D. G. COLIN-JONES, P. F. FITZPATRICK, AND R. WRIGHT (*Department of Medicine, Southampton University*) There has been recent interest in the association between coeliac disease and fibrosing alveolitis[1]. Two cases of coeliac disease associated with allergic

alveolitis due to avian exposure (bird fancier's lung) have been reported[2,3]. An increased incidence of avian precipitins amongst adult coeliac patients is recognized[4], though this could be explained on the basis of absorbed dietary antigens.

In this study we have screened 16 patients with documented bird fancier's lung for evidence of coeliac disease. Eight were selected for further investigation. Five of these patients demonstrated a severe degree of villous atrophy on jejunal biopsy, in four of whom the coeliac disease responded to a gluten-free diet. One patient failed to respond, but has improved on a poultry-free diet.

Two patients had normal jejunal histology and one patient awaits biopsy.

We feel that undiagnosed coeliac disease should be considered in cases of bird fancier's lung. In addition the association between the two conditions requires further study.

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Subcellular fractionation studies on jejunal biopsies from control subjects and from patients with coeliac disease[1]

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Although there have been several morphological studies of the intestinal lesion in coeliac disease little is known of the quantitative changes in the various subcellular organelles. Using the technique of sucrose or sorbitol density gradient centrifugation in the Beaufay automatic zonal rotor in conjunction with highly sensitive assays for marker enzymes of the individual organelles, a technique has been established for the fractionation of jejunal biopsy specimens. In control tissue the following organelles, with assigned marker enzymes and modal density between parentheses, were characterized: brush borders (alkaline phosphatase, leucyl-β-naphthylamidase, neutral α-glucosidase, α-glutamyl transpeptidase, maltase, lactase and sucrase, 1·21); lysosomes (N-acetyl-β-glucosaminidase, acid β-galactosidase, acid phosphatase, 1·20); peroxisomes (catalase, 1.19); lysosomes (acid diesterase, cathepsin C, β-glucuronidase, acid phosphatase, 1.18); mitochondria (glutamate and malate dehydrogenases, monoamine oxidase, 1.17); microsomes (alkaline α-glucosidase, 1,16); basal-lateral membranes (5'nucleotidase, 1.12) and cytosol (lactate dehydrogenase).

In biopsies from patients with untreated coeliac disease the most striking alteration was the loss of the brush border component at 1.21 density with persisting low levels of enzyme activity in the microsomal region of the gradient. The other organelles showed little change except for increased levels of free lysosomal enzyme activity indicating enhanced fragility of this organelle. The specificity of the abnormalities was indicated by the failure to demonstrate similar changes in a variety of other small intestinal diseases.

The coeliac patients were treated by gluten withdrawal or with corticosteroids and the jejunal biopsies studied sequentially. The brush border and lysosomal changes returned towards normal although the biochemical response, particularly of the brush border, was considerably slower than the morphological response or the clinical improvement.

It is concluded that analytical fractionation of jejunal biopsies leads to a clearer understanding of the subcellular pathology of the coeliac lesion and may be useful in assessing the response to therapy.

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The effects of prednisolone on the function, biochemistry and structure of the rat small intestinal mucosa[1]

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Oral prednisolone has been used successfully to treat patients with coeliac disease, Crohn's disease and various non-specific small intestinal disorders. The therapeutic mechanism of action is not clear but it has been suggested that corticosteroids may act by inducing digestive enzymes of the brush border, by stabilizing disordered lysosomal membranes, or alternatively by suppressing immune mechanisms. Studies were therefore undertaken to investigate the effects of prednisolone on the normal small intestinal mucosa. Adult male Wistar rats were given oral prednisolone-21-phosphate, 0·75 mg/kg body weight daily for seven days, and compared with pair-fed controls.

Intestinal function was assessed by examining the kinetics of *in-vivo* D-galactose absorption in 30 cm segments of proximal jejunum and distal ileum. There was a significantly greater maximum absorptive capacity (V_{max}, μmoles/cm/hr) in both the jejunum (48·1 ± 4·6 (SEM); 30·2 ± 4·7, $P = 0.007$) and the ileum (11·1 ± 1·8; 6·4 ± 1·2, $P = 0.029$) of the steroid-treated animals. The apparent affinity of the carrier for galactose (Km) was not significantly altered. By expressing the absorption per enterocyte[2] it was shown that this increase in V_{max} is due to an enhanced absorptive capacity of the individual enterocytes and not to an increased number of cells. Marker enzymes for the principal subcellular organelles were assayed in isolated jejunal and ileal enterocyte preparations. Activities (mUnits/mg DNA) of brush border (leucyl-β-naphthylamidase, neutral α-glucosidase, β-glucosidase), basal-lateral membrane (5'nucleotidase) and mitochondrial (cytochrome oxidase, malate dehydrogenase) enzymes, in addition to RNA (mg/mg DNA), were all significantly increased in the steroid-treated group. There were no changes in the levels of protein, lysosomal (N-acetyl-β-glucosaminidase, α-mannosidase, α-galactosidase) or peroxisomal (catalase) enzymes.

Comparison of the villous height, crypt depth and number of enterocytes per length of villus showed only small differences between the two groups. Autoradiography after parenteral administration of ^3H thymidine showed no change in the rate of enterocyte migration or cell turnover in the jejunum but both were slightly enhanced in the ileum.

These data show that a pharmacological dose of prednisolone enhances the absorptive and digestive capacities of the normal small intestine and suggest that these effects are due to a direct action on the enterocyte.

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Complement dependence of IgA antibody production

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It has been shown previously that IgA production is thymus-dependent at least when the antigenic stimulus is administered parenterally[1]. In this study we have examined the role of complement in the production of an IgA antibody response.

The effects of parenteral and oral immunization were studied in groups of normal inbred mice and in paired animals in which complement had been depleted *in vivo* by the use of cobra factor[2]. In one set of experiments six days after intraperitoneal injection of 5×10^8 sheep erythrocytes the number of antibody-forming cells of different classes in the spleens of control mice was as follows: IgA, 354 ± 98 (mean $\pm$ standard deviation); IgG, 1132 ± 327; IgM, 308 ± 39. In test mice, in which the plasma C3 had been reduced to less than 5% of normal by cobra factor, the numbers of antibody-forming cells were IgA, 36 ± 13; IgG, 144 ± 52; IgM, 132 ± 28. In further experiments nine days after starting oral administration of sheep erythrocytes the numbers of IgA antibody-forming cells in the spleens of control and decomplemented mice were: controls, 238 ± 64; complement-depleted, 18 ± 9. Thus, irrespective of the route of antigen administration, the production of specific IgA antibodies was suppressed in complement-depleted mice.

These results show that the complement system plays an important part in the induction of the IgA antibody response. The possible role of complement and of complement receptor lymphocytes (which form the majority of cells in Peyer's patches) in the induction of immunological responses in the intestine will be discussed.

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Characterization of the collagen of normal and cirrhotic human liver

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Chronic liver disease resulting from alcohol or hepatitis virus is invariably accompanied by collagen deposition, and there is no doubt that some of the complications of hepatic cirrhosis are directly the result of fibrosis. We have therefore undertaken a study of the nature of the collagen, in particular the genetic type and mode of crosslinking in normal liver, and their variation with age and pathological conditions.

The finding that genetically distinct collagens occur in the same tissue is a relatively recent one. Fractional precipitation of pepsin-solubilized liver collagen revealed the presence of two polymorphic forms and these were identified as type I and type III by SDS acrylamide gel electrophoresis, CM-cellulose chromatography, molecular sieve chromatography and amino-acid analysis. The relative proportion of type III was found to decrease with age. In contrast proliferation of type III collagen occurred in chronic active hepatitis.

In normal subjects, the liver collagen became increasingly resistant to pepsin digestion with increasing age, while the liver with ongoing cirrhosis was rapidly digested, indicating a change in the type of crosslinks. Hepatic collagen from young subjects was shown to be stabilized by the reducible crosslinks hydroxylysino-5 keto-norleucine and dehydrohydroxylysinonorleucine, both of which decreased with age as previously demonstrated in other tissues. Fibrotic livers from a mature subject with chronic active hepatitis revealed the presence of the stable hydroxylysino-5 keto-norleucine as the major collagen crosslink. In addition the borohydride reduction technique revealed the presence of elastin crosslink, indicating the simultaneous synthesis of new elastin in the vessels.

Our investigations indicate proliferation of type III collagen, normally present in young liver, in response to liver injury in mature subjects, and a change to a more stable type of crosslink. Similar studies are being undertaken with other cirrhotic livers of different aetiology.

Abnormal fibrin monomer polymerization in liver disease

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Although plasma fibrinogen levels in acute and chronic liver disease are usually within the normal range a prolonged thrombin time is frequently found. Isolated reports of an acquired abnormal fibrinogen with impaired fibrin monomer polymerization, mainly in patients with hepatoma, exist in the literature but the precise incidence of this abnormality remains unknown.

We have studied polymerization of fibrin monomers in 121 patients with acute or chronic hepatocellular dysfunction. Sixteen of 32 patients with cirrhosis and seven of 15 with chronic active liver disease had gross impairment of fibrinogen polymerization. This abnormality was also observed in all eight patients with acute liver failure and in two of three patients with primary liver tumour. Most of the cirrhotic patients with bleeding gastrooesophageal varices who exhibited this abnormality subsequently died as a result of continued haemorrhage. None of the 26 patients with surgical obstructive jaundice or 37 patients with hepatocellular dysfunction secondary to systemic disease demonstrated the abnormality.

It is concluded that impaired fibrin monomer polymerization is common in acute and chronic liver disease and that its presence correlates with the prognosis in patients with bleeding varices. It appears to provide a useful test to assist in the differentiation of obstructive from hepatocellular jaundice.

A simple test for patency of portacaval shunts

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Methods available for testing the patency of portacaval shunt procedures are all expensive, tedious or dangerous; for example, the EEG response to a protein meal or ammonium chloride or inferior vena cavography. We have developed a simple test which may be useful in this situation. Glucagon increases both urinary and plasma cyclic 3-5 adenosine monophosphate (cAMP)[1], and the source of this nucleotide is primarily the liver[2]. We have studied the plasma cAMP response to 1 mg of intravenous glucagon

in 10 normal volunteers and in patients with liver pathology.

In 10 normal volunteers the plasma cAMP released in the first hour after injection as measured by the area under the response curve was 16·6 ± 1·7 Units. In 10 patients with cirrhosis of varying aetiology and degree of portal hypertension the amount of cAMP released was 23·3 ± 3·8 which is not significantly different from the normals. In seven patients with cirrhosis and end-to-side portacaval shunts the cAMP response was abnormally low, being only 1·8 ± 1·4 ($P = 0.01$). The range of response was from zero to 60%. In one patient with a shunt which was no longer patent the response was normal.

We conclude that after portacaval shunt procedures the hepatic cAMP response to glucagon either does not occur or is not reflected in the plasma while the shunt is patent. This simple outpatient test may prove useful in the assessment of shunt size and patency.

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Lymphocyte cytotoxicity for kidney cells in the renal tubular acidosis of autoimmune liver disease

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Multisystem involvement, especially renal tubular acidosis, is a common finding in patients with autoimmune liver disease, and in such patients we have recently shown sensitization to Tamm-Horsfall glycoprotein (THGP), a tubular kidney antigen. To investigate whether this immune reaction could be damaging to renal tubular cells we have studied lymphocyte-mediated cytotoxicity to baby hamster kidney cells, which are known to produce THGP in culture. Highly purified lymphocytes from patients with either chronic active hepatitis or primary biliary cirrhosis were added to kidney cells in microplates at a ratio of 400:1. After 48 hours' incubation the number of kidney cells remaining in the test, compared with control wells, was expressed as the percentage cytotoxicity.

Lymphocytes from eight of the 18 patients tested were cytotoxic to kidney cells, including all of the six with renal tubular acidosis. The addition of THGP to the chambers blocked the cytotoxic reaction, showing that the kidney cell damage was due to sensitization to this antigen.

We have already shown that there is a glycoprotein in the hepatocyte plasma membrane which crossreacts with THGP, and the present results suggest that sensitization to this antigen, initiated by the liver injury, may damage renal tubular cells and produce the acidification defect.

Lymphocyte populations in chronic liver disease

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Lymphocyte populations in the peripheral blood of patients with chronic active hepatitis (CAH), alcoholic hepatitis (AH) and primary biliary cirrhosis (PBC) were studied using rosetting techniques.

T cell concentrations were significantly depressed in all patient groups. This was slight in PBC, moderate in HB_sAg-positive CAH and AH and most marked in HB_sAg-negative CAH. Lymphocytes forming rosettes with antibody-coated erythrocytes were normal in AH, PBC and HB_sAg-positive CAH, but decreased in HB_sAg-negative CAH. 'Null' cells bearing neither the receptor for sheep erythrocytes (T cells) nor antibody-coated erythrocytes (B and K cells) were increased in patients with AH and HB_sAg-positive and -negative CAH. Some null cells may be related to coating of lymphocytes with antibody, for eight of 20 patients with HBsAg-negative CAH showed serum antilymphocyte antibody; this was not found in HB_sAg-positive CAH patients.

Levamisole resulted in a significant reduction in null cell concentration and an increase in T cell numbers in CAH and AH. This suggests that some null cells are immature T cells. Activated T cells, measured by an auto-rosette technique, were not increased in these patients.

CONCLUSION

T cell concentrations are significantly depressed in chronic liver disease, particularly HB_sAg-negative active chronic hepatitis. Null cells (lymphocytes which are neither T nor B cells) were increased in alcoholic hepatitis and HB_sAg- positive and -negative hepatitis and some of these cells are immature T cells. In HB_sAg-negative chronic active hepatitis, some null cells may also be due to coating of lymphocyte with antibody.

Antipyrine, lingocaine and paracetamol metabolism in chronic liver disease

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Plasma half-lives of drugs metabolized in the liver by hydroxylation (antipyrine), N-dealkylation (lignocaine) and conjugation (paracetamol) were measured in 19 patients (11 females, eight males: aged 26-68 years) to determine the effects of chronic liver disease on different routes of drug metabolism. Diagnoses were established by routine methods, including liver biopsy or necropsy (alcoholic cirrhosis 10, cryptogenic cirrhosis 2, primary biliary cirrhosis 3, chronic active hepatitis 2, sclerosing cholangitis 1, nodular transformation 1). Single oral doses of antipyrine (18 mg/kg), lignocaine (400 mg) and paracetamol (1·5 g) were given on separate days and blood and urine samples collected regularly. Drug concentrations were estimated by gas-liquid chromatography.

Antipyrine half-life was abnormal in nine of 15 patients (mean 32·9 hr, range 4·9-137 hr; normal 12 ± 0·5 hr) and paracetamol half-life was abnormal in 10 of 14 (mean 3·15 hr; range 1·5-7.0 hr; normal 2·0 ± 0·1 hr). Lignocaine half-life was prolonged in 15 of 16 patients (mean 7·3 hr, range 1·8-19 hr; normal 1·4 ± 0·01), with increased urine excretion of unchanged lignocaine and reduced excretion of metabolites.

Each drug half-life correlated with serum albumin and prothrombin ratios but not with transaminase, alkaline phosphatase or bilirubin estimations. Thus impaired drug metabolism correlates with disease severity.

Marked prolongation of the half-life of one drug was always associated with impaired metabolism of the others (lignocaine/paracetamol $r = 0.89$, anti-

pyrine/paracetamol r = 0·95, lignocaine/antipyrine 0·94). Lignocaine metabolism was always the most depressed and is a highly sensitive index of liver disease.

Response to jejunal acidification in patients with duodenal ulcer and normal subjects

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The jejunal disposal of perfused acid was studied in eight control subjects and 10 duodenal ulcer (DU) patients and related to the gastric, pancreatic and cholecystokinetic responses. Duodenal ulcer patients disposed of acid less well than control individuals and required on average an 8·4 cm longer segment of jejunum than the controls to dissipate the same quantity of acid. Acid disappearance was accompanied by jejunal secretion of water, sodium, potassium and chloride with secretion of more chloride than control by patients with duodenal ulcer. The DU patients secreted more trypsin and less bicarbonate into the duodenum than control subjects. Jejunal acidification inhibited the pancreatic enzyme-secretory response to intravenous secretin plus CCK in control subjects but not in patients with duodenal ulcer. We conclude that the whole upper small intestine in duodenal ulcer patients responds abnormally to acid. Duodenal ulcer patients probably release more CCK-like and less secretin-like hormones than normal subjects in response to acid in the jejunum.

A controlled comparison of highly selective vagotomy against truncal vagotomy and pyloroplasty for duodenal ulcer

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Since July 1973, 90 male patients being treated selectively for chronic duodenal ulceration have been admitted to a randomized comparison of highly selective vagotomy (HSV) and truncal vagotomy and pyloroplasty (TVP). There has been no operative death and morbidity in the two groups was similar, in contrast to the increased wound sepsis found after TVP in an earlier comparison[1]. Functional results (Visick grading) at an average follow up of one year show no statistically significant difference although a smaller number have poor or fair results after HSV. One proven recurrent ulcer has been found after HSV and two suspected. After TVP two suspected recurrent ulcers occurred. All four had negative endoscopy. Diarrhoea was less after HSV (8%) than after TVP (22%) but none was troublesome.

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Interim results of a prospective randomized trial of highly selective vagotomy versus a more proximal type of gastric vagotomy for duodenal ulcer: Clinical and secretory findings

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Contrary to initial expectation, HSV without a drainage procedure is not devoid of side effects. It impairs accommodation by gastric smooth muscle and this produces abnormal intragastric pressure after meals and accelerated emptying of liquids[1]. Symptoms such as postprandial discomfort and early dumping may result. In HSV, only about 6 cm of stomach remain innervated, whereas when the extent of the antrum is mapped at operation[2] 10 cm on average can be left innervated and side effects may be fewer.

After an initial pilot study, consecutive DU patients were 'randomized' in the past three years to either HSV (n = 44) or to a more 'proximal vagotomy' ('PV') (n = 43) in which the distal 10 cm of stomach was left innervated. We wished to find out whether the more proximal vagotomy would produce fewer side effects, at acceptable risk.

The acid response to insulin (PAOI-BAO) one week after operation was found to be significantly greater after 'PV' than after HSV (mean ± 1SE, 1·3 ± 0·5, cf 0·2 ± 0·2, m-equiv/hr) and 36% of 'PVs' were incomplete by Hollander's criteria compared with 15% of HSVs. The clinical results in the two groups did not differ significantly (88% Visick grades 1 + 2 in each group), but postcibal fullness was noted in 30% of patients after HSV compared with 15% after 'PV'. Early dumping was noted in 0% after HSV and 4% after 'PV'.

These findings suggest that any reduction in side effects as a result of leaving more of the stomach innervated might be secured at the price of a higher incidence of recurrent ulceration. So far, however, no patient has developed recurrence after 'proximal vagotomy'.

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Metabolic studies after Billroth I gastrectomy and highly selective vagotomy for gastric ulcer

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It is no longer obvious that Billroth I(B-I) gastrectomy is the operation of choice for a patient with gastric ulcer (GU). Even in skilled hands, operative mortality may be as high as 5%[1], the incidence of recurrence at five to 10 years is 4 to 5%[1,2] and only 72 to 78%[1,2] of patients enjoy a really good functional result. Preservation of the terminal antrum and pyloric sphincter, as in the 'Maki' gastrectomy[3] or HSV, permits better regulation of gastric emptying and possibly better intestinal absorption.

In patients who had undergone either B-I (n = 10) or HSV (n = 12) for GU at least one year previously, we measured faecal outputs of fat, nitrogen, iron and calcium over an eight-day period on a metabolic ward where intakes could also be measured precisely. A non-absorbable marker (PEG) was used. Faecal fat output was found to be significantly greater ($P < 0.05$) after B-I than after HSV. None of the HSV patients had steatorrhoea (> 6g faecal fat per day) whereas 30% of the B-I patients had steatorrhoea, which was gross in two. No significant differences were found between the two groups with respect to faecal outputs of nitrogen, iron or calcium. Impaired capacity for food was noted in three of the B-I patients but in none of the patients after HSV.

These findings suggest that, in the long term, patients who are treated by HSV for benign gastric ulcer will be better nourished than patients who undergo Billroth-I gastrectomy.

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The pentagastrin-insulin secretion test: Its value in diagnosis and surgical management of recurrent ulceration following previous vagotomy

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The Hollander insulin test remains the usual investigation in recurrent ulceration following earlier vagotomy and drainage. Yet the test gives no information on either the secretory capacity of the stomach or the relevance of any residual vagal function demonstrated. To answer these disadvantages a combined pentagastrin-insulin test was described in 1970 and the present paper reports the long-term results obtained with the test.

Three study groups have been analysed:

Group A, 110 patients investigated before and after vagotomy and Polya for DU between 1968 and 1972 who in 1974 were free of any residual dyspepsia;

Group B, 44 patients investigated for symptoms following earlier vagotomy and drainage who did not have recurrent ulcers on endoscopy;

Group C, 83 patients with surgically or endoscopically confirmed recurrent ulcers.

Group C patients were found to have significantly higher acid and pepsin outputs ($P < 0.05$) than group B and there was a relatively higher pepsin output relative to acid as had been found in a similar analysis of 'active' duodenal ulcer.

When the insulin responses of acid (A) and pepsin (P) to those after pentagastrin were expressed as a percentage ratio the patients could be divided into three goups: I = A < 45%, P < 100%; II = A > 45%, P < 100%; III, A > 45%, P > 100%.

When applied to the study groups the distribution was as follows: group A before vagotomy, I 4%, II 9%, III 87% and after vagotomy, I 70%, II 23%, III 7%; group B I 54%, II 34%, III 12%; group C I 24%, II 24%, III 52%.

Follow up of 27 patients treated surgically between 1968 and 1972 revelaed that further ulcers had developed in two patients. One had been in group I and had had a re-vagotomy and one in group III who had had a gastrectomy.

These results suggest that this test may prove of considerable value in assessment of recurrent ulceration and should be more widely applied.

Double-blind controlled trial of cholestyramine in the treatment of postvagotomy diarrhoea

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No satisfactory treatment is at present available for postvagotomy diarrhoea. It has recently been shown that patients with severe, continuous postvagotomy diarrhoea have increased faecal levels of bile acids, particularly chenodeoxycholic acid[1]. It has been suggested that the bile acid-binding resin, cholestyramine, may be of value in the management of this condition[2].

A double-blind controlled trial of cholestyramine has been performed in a group of these patients. Eight patients with severe, continuous postvagotomy diarrhoea were given 4 g of cholestyramine per day for two months and eight similar patients were given a placebo for a similar time. The two groups of patients were reviewed, two four and eight weeks after starting therapy and haematological and biochemical indices checked before treatment and at each review. A scoring system was devised to assess response in terms of reduction in number of stools, consistency, and presence or absence of urgency.

A significant improvement was recorded in patients receiving cholestyramine, but no overall improvement was observed in the placebo group. No side effects were noted during treatment and no haematological or biochemical upsets occurred.

This trial indicates that cholestyramine may be of value in the treatment of intractable postvagotomy diarrhoea.

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Endoscopic pancreatography, scintigraphy and exocrine function in pancreatitis: A comparative study

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Seventy-three patients with a diagnosis of acute or relapsing pancreatitis were investigated by endoscopic retrograde choledochopancreatography (ERCP)[1].

Forty-eight of these patients, who were suspected clinically of having chronic pancreatitis, were in addition subjected to a secretin stimulation test and a Lundh test and 37 patients to a dynamic (^{75}Se) selenomethionine scan employing a gamma camera. The pancreatograms were assessed independently by two observers, each having experience of more than 500 endoscopic pancreatograms. Pancreatograms were graded as follows: minimal-change pancreatitis (MCP), moderate pancreatitis, or severe pancreatitis according to the criteria of Kasugai *et al* (1974)[2]. These results were compared with the maximum bicarbonate volume and duodenal trypsin following the secretin and Lundh tests respectively.

Twenty-nine of 48 patients demonstrated abnormal pancreatograms. Whilst both the secretin and Lundh tests showed a correlation with the changes shown by pancreatography the Lundh test was abnormal in 10 of 12 cases of minimal change pancreatitis, as opposed to the maximum bicarbonate being abnormal in only four of 12 cases. The secretin test correlated well, however, with moderate three out of five and severe 12 of 13 pancreatitis as judged by pancreatography and gave an accurate indication of main duct obstruction (six of seven). Both tests gave an accurate assessment of a normal gland as judged radiographically.

The selenomethione scans were analysed by one experienced observer (RD) without knowledge of the other investigations. Thirty of 31 abnormal pancreatograms had reduced (^{75}Se) selenomethionine activity but there was no correlation between the degree of reduced activity and pancreatogram grading. On the other hand four of six normal pancreatograms also had normal scans.

These results suggest that endoscopic pancreatography correlates well with standard exocrine function tests and that minimal-change pancreatitis is a significant entity and can be detected both by radiology and by duodenal trypsin assay.

In addition, dynamic pancreatic scans, when analysed by an experienced observer, accurately indicate a normal or an abnormal gland but cannot judge the severity of pancreatitis.

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A randomized trial of percutaneous transhepatic cholangiography versus endoscopic retrograde cholangiography for bile duct visualization in cholestasis

E. ELIAS, A. N. HAMLYN, S. JAIN, R. LONG, J. A. SUMMERFIELD, R. DICK, AND S. SHERLOCK (*Departments of Medicine and Radiology, Royal Free Hospital*) Percutaneous transhepatic cholangiography (PCC) using the narrow Chiba needle[1] has been compared with endoscopic retrograde cholangiography (ERC). Fifty-one patients with cholestasis were randomly assigned to either PCC or ERC. The alternative procedure was used when the first had failed or when the information obtained was incomplete. The final diagnoses reached were PBC (14 patients), gallstones (10), carcinoma of the pancreas or bile ducts (9), postoperative stricture of the bile duct (5) and miscellaneous other disorders (3).

When used as the initial procedure PCC was successful in 12 of 25 (48%) and ERC in 16 of 26 (62%). When the 23 failures were investigated by the second technique the bile ducts were visualized in a further 17 giving an overall success rate of 88% for the series.

Patients with dilated intrahepatic bile ducts showed a 94% (15 of 16) success rate with PCC and a 71% (12 of 17) success rate with ERC. When ducts were not dilated the success rates were 24% (five of 21) for PCC and 70% (16 of 23) for ERC.

Antibiotics were administered routinely to PCC patients and following ERC if obstruction to the biliary system was seen. A leak of bile into the peritoneum occurred in one patient following PCC, and one patient developed suppurative cholangitis after ERC. There were no other complications.

It is concluded that since PCC with the Chiba needle is a safe procedure, less costly than ERC, requires less expertise, and has a very high rate of success in visualizing the bile ducts when they are dilated, it should be the procedure of first choice in the investigation of cholestasis.

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Oestrogen metabolism in chronic liver disease: A new lead

J. R. B. GREEN, N. A. G. MOWAT, R. A. FISHER, D. C. ANDERSON, AND A. M. DAWSON (*Departments of Gastroenterology, Chemical Pathology and Medicine, St. Bartholomew's Hospital, London*) Although abnormal oestrogen metabolism has been assumed to be the cause of feminization in males with chronic liver disease[1], the results are contradictory. This is due to the lack of specificity of the assay procedures used and also to insufficient sensitivity of the techniques to measure the low concentrations of oestrogen normally found in male plasma. In addition, all reports have concerned only oestradiol, the main biologically active oestrogen.

We have developed a sensitive and specific assay for measurement of the three principal unconjugated oestrogens in male plasma—oestrone, oestradiol, and oestriol. This involves prior celite chromatography followed by radioimmunoassay. In addition we have been able to measure the free (unbound) concentrations of oestradiol.

With these methods, we have studied 25 patients with chronic liver disease of different aetiologies, approximately half of whom had gynaecomastia. The major abnormality of oestrogen metabolism that we have shown is significantly raised plasma oestrone concentrations in patients with gynaecomastia when compared to non-gynaecomastia patients or normal controls We have so far shown no abnormality or free plasma oestradiol or total plasma oestriol. Oestrone is the major precursor of oestradiol and the significance of this finding in relation to feminization is discussed.

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The 24-hour control of intragastric pH by cimetidine, a new H_2-receptor antagonist, in normal subjects and in patients with duodenal ulcer

R. E. POUNDER, J. G. WILLIAMS, J. J. MISIEWICZ AND G. J. MILTON-THOMPSON (*Royal Naval Hospital, Plymouth, and Medical Research Council Gastroenterology Unit, Central Middlesex Hospital, London*) Recording intragastric pH by sampling hourly through a nasogastric tube allows the effects of drugs on gastric acidity to be measured during prolonged periods in subjects with virtually unrestricted activity who eat normal meals. The method was used to study the effect of cimetidine[1] on 10 normal volunteers and six patients with duodenal ulcer. Gastric acidity was measured continuously during 48 hr with 24 hr placebo and treatment days randomly allocated. Meals, fluid and alcohol intake and cigarette consumption were the same each day. The pH of gastric contents was measured on 5 ml aspirates with a combined glass electrode. Blood cimetidine levels were measured chromatographically and plasma gastrin by radioimmunoassay[2].

Replicate studies with placebo on one normal subject correlated well ($r = 0{\cdot}8$). In normals the effects of taking cimetidine 0·8 or 1·0 g/day before or after meals were investigated. Preprandial medication resulted in faster drug absorption with higher blood levels (4-6·4 μmol/ml) but mean intragastric hydrogen ion concentration was lower ($P < 0{\cdot}04$) than during the placebo day in only two sampling periods. The same dose after meals lowered ($P < 0{\cdot}05$ to $0{\cdot}01$) gastric acidity in eight sampling periods and blood concentrations were better sustained. Mean fasting plasma gastrin rose ($P < 0{\cdot}01$ to $0{\cdot}02$) from prestudy ($19{\cdot}54 \pm 3{\cdot}40$ pg/ml) and postplacebo ($18{\cdot}44 \pm 2{\cdot}43$ pg/ml) levels to $25{\cdot}55 \pm 4{\cdot}06$ pg/ml after cimetidine. In patients with duodenal ulcer postprandial cimetidine 0·8 g/day lowered gastric acidity ($P < 0{\cdot}05$) in five but 1·6 g/day lowered it ($P < 0{\cdot}05$ to $0{\cdot}025$) in 11 sampling periods.

The results indicate that cimetidine should be administered after meals, that a dose of 1·6g/day or more may be needed consistently to reduce gastric acidity, and that the effects of treatment on gastrin secretion need surveillance.

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Transfer factor in the treatment of Crohn's disease

P. ASQUITH, E. MALLAS, I. ROSS, R. D. MONTGOMERY, W. T. COOKE, AND R. A. THOMPSON (*The Department of Experimental Pathology, University of Birmingham, The Nutritional and Intestinal Unit, The General Hospital, Birmingham, and The Regional Immunology Laboratory, East Birmingham Hospital, Birmingham*)
Transfer factor (TF) is a dialyzable extract of immune leucocytes capable of transferring cellular immunity from a skin test-positive donor to a skin test-negative recipient (Lawrence 1949). Transfer factor prepared from healthy blood donors has been used in the treatment of seven patients with Crohn's disease—four with diffuse involvement of small and large bowel disease and enterocutaneous fistulas and three with diffuse small bowel disease. Five had been treated with ACTH and two with azothioprine without controlling the disease. Transfer factor was administered at intervals from one to four weeks over two to nine months and the response assessed clinically, haematologically, biochemically and immunologically, including repeated skin tests with tuberculin, candida and trichophyton, serial quantitation of T and B cells, PHA, Con A and PWM responsiveness, and serum immunoglobulin levels. Clinical and biochemical improvement together with change in skin tests in six patients and decreased PHA and increased PWM reaction occurred. These preliminary results are sufficiently encouraging to warrant further trials.

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Treatment of ulcerative colitis with disodium cromoglycate: A long-term double-blind clinical trial

V. MANI, G. LLOYD, F. GREEN, H. FOX, AND L. A. TURNBERG (*Division of Gastroenterology, Manchester Royal Infirmary, and Department of Pathology, University of Manchester*)
Disodium cromoglycate (DSCG) interferes with the release from mast cells, sensitized with IgE, of a number of substances responsible for the manifestations of acute (type I) allergic reactions. It has been found to be of considerable benefit in the treatment of allergic asthma. It is conceivable that mast cells may mediate some of the manifestations of ulcerative colitis and a therapeutic trial with disodium cromoglycate was undertaken on the basis of this possibility. A double-blind, cross-over study was carried out in 12 patients with proctocolitis. Disodium cromoglycate (2 g/day) or placebo was given orally for six months followed by six months on the alternative therapy. Results were analyzed according to criteria laid down for general well being, stool frequency, rectal bleeding, sigmoidoscopic appearance, and rectal biopsy appearance. Histological sections from each patient's biopsies were examined blind by two pathologists. The results demonstrated a statistically significant therapeutic benefit in favour of disodium cromoglycate in each aspect examined, including the histological appearance. There was no obvious change in the mast cell population. One patient not included in this analysis developed modestly raised transaminases and his therapy was stopped.

We conclude that oral disodium cromoglycate may be of benefit in the long-term management of ulcerative colitis.

Bacterial breakdown of sulphasalazine (Salazopyrin)

A. K. AZAD KHAN, H. H. JOHNSTON, AND S. C. TRUELOVE (*Nuffield Department of Clinical Medicine and Public Health Laboratory, Radcliffe Infirmary, Oxford*)
Sulphasalazine is effective in reducing the relapse rate in ulcerative colitis[1, 2]. After ingestion sulphasalazine passes into the colon largely unchanged and there the azo-linkage is broken by the colonic bacteria to release sulphapyridine and 5-aminosalicyalic acid[3].

We have compared the capacity of various bacterial species to split the azo-linkage of sulphasalazine *in vitro* and have defined the conditions necessary for optimal action. All the bacterial species used were grown from faeces and included strains of *Escherichia coli*, *Klebsiella aerogenes*, *Streptococcus faecalis*, *Pseudomonas pyocyanea* and bacteroides species. None of these strains was capable of breaking the azo-linkage when tested in phosphate buffer. However when FAD, NADP and G-6-PO_4 were added, rapid breakdown occurred. There were no marked differences in the activity of the various species, although *Streptococcus faecalis* was relatively inactive. Sonically disrupted bacteria showed greater activity than intact bacteria. No activity could be detected in the fluid in which the bacteria were suspended. The activity was greater if sonically disrupted cells were incubated anaerobically than aerobically.

From this we conclude that: (1) The enzyme responsible for breakdown of the azo-linkage needs FAD and NADPH. (2) The enzyme is located within the bacterial cells. (3) The enzyme is inhibited by the presence of oxygen.

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Changes in human colonic mucus in ulcerative colitis

G. M. FRASER AND J. R. CLAMP (introduced by Professor A. E. Read, *Department of Medicine, University of Bristol, Bristol*)
Mucus depletion of the colonic epithelium is one of the histological features of ulcerative colitis[1].

The purpose of this study was to investigate colonic mucus preparations from normal individuals and from patients with ulcerative colitis. Water-soluble glycoproteins were prepared from mucosal scrapings from normal and colitic colons and subjected to exclusion chromatography on Sepharose 2B columns. Two fractions were obtained. The first fraction (S-1) was excluded and had a carbohydrate content of 33·0 ± 5·6% (by weight) whereas that from patients with ulcerative colitis was 16·1 ± 4·1%. This fraction contained monosaccharides characteristic of mucous glycoproteins and had molar proportions of fucose:mannose:galactose:*N*-acetylglucosamine : *N*-acetylgalactosamine : sialic acid of 2·4:0·3:6·0:7·2:7·6:6·2 which was not significantly different to the values in ulcerative colitis, namely, 1·9:0·8:6·0:6·9:7·4:6·8. The oligosaccharide units in mucous glycoproteins are linked to the protein core through *N*-acetylgalactosamine by an 0-glycosidic link to serine and threonine[2]. The combined serine and threonine content of fraction S-1 was 18·3 moles/100 moles amino acids in normals

whereas active ulcerative colitics had a significantly lower value of 9·6 moles/100 moles. Possibly the lower content of serine and threonine and, therefore, the reduced number of sites available for 0-glycosidic linkage may account for the reduction in the percentage weight of carbohydrate found in the S-1 fraction in ulcerative colitis.

A second fraction (S-2), which was retarded on Sepharose 2B columns, had molar proportions of fucose:mannose: galactose : *N*-acetylglucosamine : *N*-acetylgalactosamine:sialic acid of 2·7:3·1:6·0: 6·2:3·5:2·9 in normals and 2·5:5·5:6·0:5·4: 4·9:3·0 in active ulcerative colitics. The mannose content of the S-2 fraction in active ulcerative colitics is significantly increased ($P < 0.01$) over that of normals.

It is therefore concluded that there are changes in colonic mucosal glycoproteins in active ulcerative colitis affecting the overall composition of both carbohydrate and amino acids.

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Glucosamine synthetase activity in the colonic mucosa in ulcerative colitis and Crohn's disease

M. J. GOODMAN, P. W. KENT, AND S. C. TRUELOVE (*Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford*) The enzyme glucosamine synthetase (GmS, L-glutamine-D-fructose-6-phosphate aminotransferase) catalyses the synthesis of glucosamine, which is probably a rate-limiting reaction in the biosynthesis of gastrointestinal mucus. In the rectal biopsies of 20 patients with the irritable colon syndrome and in normal mucosa from 25 colectomy specimens for carcinoma and diverticulitis, the GmS levels were 13·8 ± 4·0 (SD) units (μmoles glucosamine synthesized/h/g wet wt under standard conditions), with little or no GmS in the submucosa.

In 36 samples of mucosa taken from 12 colectomy specimens with inflammatory bowel disease, the GmS levels correlated with the epithelial cell density rather than with the goblet cell density. In 15 patients recovering from acute attacks of ulcerative colitis, the GmS levels in serial rectal biopsies rose to a peak of 23·9 ± 4·1 units. Thus the GmS level in colonic mucosa usually reflects the epithelial cell density but disproportionately high levels are found in healing mucosa.

In the histologically normal rectal biopsies of 13 patients who had suffered from Crohn's disease elsewhere in the bowel, some of whom had had resections, the GmS levels were 20·6 ± 5·2 units, a highly significant elevation above the normal. This suggests that the apparently normal mucosa in Crohn's disease has an abnormal biochemical activity.

Serum and tissue immunoglobulins in patients with chronic proctitis

R. V. HEATLEY, R. H. WHITEHEAD, J. RHODES, B. J. CALCRAFT, AND R. FIFIELD (*University Department of Surgery and Department of Gastroenterology at the University Hospital of Wales and the Department of Medical Biochemistry, Cardiff Royal Infirmary*) It has frequently been suggested that an allergic mechanism may play a role in the pathogenesis of ulcerative proctocolitis. The eosinophilic infiltrate with degranulated mast cells and increased numbers of plasma cells in the gut wall support this hypothesis. Similar features are found in the bronchial wall in asthma where IgE is thought to play an important part in the pathogenesis by releasing vasoactive amines from lung tissue. This process is inhibited by disodium cromoglycate, a compound which is of value therapeutically in asthma. We have previously reported our findings in a group of patients with proctitis; many had large numbers of eosinophils in the rectal mucosa and a substantial number of these patients responded to topical treatment with disodium cromoglycate.

In an attempt to identify a similar immunological process in the rectal mucosa of patients with proctitis, we have performed serial serum immunoglobulin estimations and concurrently examined rectal biopsies by immunofluorescence for IgG, IgA, IgM and IgE.

Serum immunoglobulins were measured in 26 patients with chronic proctitis during activity of the disease and in remission. Twenty-four rectal biopsies were obtained from 14 patients with proctitis and nine biopsies from a group of control patients. They were stained with specific fluorescent antisera and examined for evidence of immunoglobulin-producing cells.

All of the serum immunoglobulins were within the normal range and showed no significant change when patients went into remission. The most significant finding from this study was an intense staining of numerous cells containing IgE in the lamina propria of rectal biopsies from patients with active proctitis (medium 37, range 4-50 + cells per high-power field); normal biopsies contained only scattered isolated IgE-containing cells. There were few IgM cells in normals (median 4, range 1-9/hpf) and rather more in proctitis (median 19, range 0-40/hpf). The corresponding figures for IgG were less than 5 cells/hpf in normals and 4, range 0-50 +, in proctitis. There was little difference in the amounts of IgA present which was not quantitated.

This study provides further evidence of the role of immune mechanisms in proctitis.

Complement in inflammatory bowel disease

H. J. F. HODGSON, B. J. POTTER, AND D. P. JEWELL (*Academic Department of Medicine The Royal Free Hospital, London*) Circulating immune complexes have been reported in patients with ulcerative colitis and Crohn's disease. Since certain types of immune complex are able to activate the complement pathway, we have investigated the metabolism of the third component of complement (C3) using ^{125}I-labelled C3 which was prepared from fresh human plasma. The purification and labelling procedures did not affect its haemolytic activity. Following intravenous injection of the ^{125}I-C3, serial blood samples were obtained during the following seven days together with 24-hr collections of urine and faeces.

Studies have been performed on five patients with active disease, not requiring urgent treatment, and compared with 10 control subjects. In all patients the labelled C3 disappeared from the plasma more rapidly than in the control subjects. The mean fractional catabolic rate (3·21 ± 0·37% iv pool/hr) and the mean synthesis rate of C3 (59·2 ± 30·6 mg/kg body wt/day) were significantly higher than the controls (2·04 ± 0·2%/hr, $P < 0.05$, and 25 ± 5 mg/kg/day, $P < 0.05$, respectively). This increased metabolism was specific for C3 since albumin metabolism studied simultaneously using ^{131}I-human serum albumin did not differ significantly from the controls.

In common with previous studies, the C3 concentrations in the patients' sera were within the normal range, but the metabolic data demonstrate that there is, nevertheless, an increased complement

consumption in patients with inflammatory bowel disease.

Abnormalities of splenic function in ulcerative colitis and Crohn's disease

F. P. RYAN, F. E. PRESTON, R. C. SMART, AND C. D. HOLDSWORTH (*Departments of Medicine, Haematology and Medical Physics, Royal Infirmary, Sheffield*) The finding in the peripheral blood film of Howell-Jolly bodies, target cells and burr cells implies either splenectomy or impairment of splenic function. In this sense, hyposplenism has long been known to complicate coeliac disease and dermatitis herpetiformis. This communication reports our finding that hyposplenism is also a relatively common complication of ulcerative colitis, but not of Crohn's disease.

Peripheral blood films from 72 patients with ulcerative colitis and 40 patients with Crohn's disease were studied for the characteristic changes. Howell-Jolly bodies were found in nine patients with ulcerative colitis but in none with Crohn's disease.

Using as a more objective test of splenic function the rate of clearance of heat-damaged ^{51}Cr-labelled red cells from the circulation, eight out of 30 colitics had impaired clearance, the most severe cases also having Howell-Jolly bodies in their blood films. Of 14 Crohn's patients tested, none had impaired clearance, while five had clearances faster than normal controls implying splenic hyperfunction. The difference between colitis and Crohn's is significant at the 1% level.

In view of the known association (in coeliac disease) of hyposplenism and lymphoreticular atrophy, and also of splenectomy and fatal septicaemia, it may be important that one patient with hyposplenism had serious pneumococcal septicaemia, while two others died from probable bacteraemic shock.

Effect of somatostatin on motilin levels and gastric emptying

S. R. BLOOM, D. N. RALPHS, G. M. BESSER, R. HALL, D. H. COY, A. J. KASTIN, AND A. V. SCHALLY (*Department of Medicine, The Royal Postgraduate Medical School, Hammersmith Hospital, London, and the Department of Surgery, The Middlesex Hospital, London*) A sensitive and specific radioimmunoassay has been developed for the new gut hormone motilin. Levels in human fasting plasma have been found to be highly variable with a mean value of approximately 100 pg/ml.

Four healthy volunteers underwent gastric emptying studies using a continuous recording gamma camera system. During somatostatin infusion (13 μg/min) gastric emptying was considerably retarded in each individual by comparison with a saline control day ($T\frac{1}{2}$ 70 $\pm$ 33% (SE) longer). Plasma motilin concentrations were also significantly suppressed in each individual (mean fall 57 $\pm$ 15%) during the somatostatin infusion. This is in accord with the proposed action of motilin in enhancing the rate of gastric emptying.

Motilin levels in 10 normal subjects after ingestion of a meal were measured and were highly variable showing a small mean rise at 20 minutes (42 $\pm$ 13 pg/ml) but a net fall at 90 minutes (-7 ± 9 pg/ml). Further work is required in elucidating the exact physiological role of this new hormone.

Neonatal hypergastrinaemia in man

A. TORSOLI, G. F. DELLE FAVE, P. MELCHIORRI, N. SOPRANZI, AND ANNA KOHN (*Gastroenterology Unit 2nd Department of Medicine and Department of Pharmacology of the University, Rome*) Previous studies in rats have shown no antral gastrin activity at birth or during suckling[1]. This activity, as well as the concentration of gastrin in antral mucosa, dramatically increases in the weaning period[1, 2]. Conversely plasma gastrin in man has been found to be significantly higher on the fourth day of life than in the mother at labour[3].

Plasma gastrin levels were therefore measured by radioimmunoassay in 25 apparently normal babies of both sexes, from the first to the seventh day of life, before (*a*) and 30 min (*b*) after feeding (humanized milk). A significant increase in the values (pg/ml) was found, in comparison with those of cord vein (114 $\pm$ 14), at 24-36 hr (*a*, 186 $\pm$ 43[4]; *b*, 209 $\pm$ 44[4]) and 96-120 hr (*a*, 290 $\pm$ 56[5]; *b*, 263 $\pm$ 52[5]). Molecular forms of circulating gastrin were identified by chromatographic separation on Sephadex in a group of five 5-day-old babies. Gastrin was represented by 45% big-big and 55% big form.

These findings confirm the existence of hypergastrinaemia in the human neonatal period. Its progressive increase until the fifth day indicates a non-maternal origin. Absence of significant variations after feeding is in agreement with results of chromatographic investigations. These data may also be of some interest for interpreting the tendency of newborn babies to gastric hypoacidity and LES incompetence.

[4]$P < 0.05$, [5]$P < 0.01$

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The diagnosis of the Zollinger-Ellison syndrome

R. C. G. RUSSELL, L. CHIAM, AND H. A. F. DUDLEY (*Surgical Unit, St Mary's Hospital, London*) Early diagnosis of the Zollinger-Ellison syndrome (ZES) reduces mortality[1]. To differentiate the causes of hypergastrinaemia a sequential approach has been developed. The basis is initial acid output studies followed by gastrin and serum calcium determinations. Thereafter stimulation tests are applied to the residue of patients still suspected of ZES. Fourteen patients have been studied and accurately classified as the ZES (9), antral G-cell hyperplasia (1), and miscellaneous (4).

Basal acid output proved a useful discriminator but an MAO/BAO ratio of 0·6 underdiagnosed the syndrome. Plasma gastrin in the suspects was bimodal (ZES 65-550 ng/l; others 60-90 ng/l). Protein stimulation produced two false negatives and secretin four false negatives in the nine Zollinger-Ellison patients. Thirteen of 14 patients showed a rise in gastrin level on calcium infusion, and discrimination, using the magnitude of rise between ZES and others, was possible in all but one.

Thus, an accurate diagnosis can be established and the correct treatment applied. This can arrest complications in ZES and avoid gastrectomy when an autonomous lesion is not present.

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The Oxo test in the diagnosis of gastrinomas, antral gastrin cell hyperplasia, and recurrent peptic ulceration

P. C. GANGULI, T. V. TAYLOR, M. MORRIS, J. B. ELDER, J. M. POLAK, AND A. G. E. PEARSE (*University Department of Surgery, Royal Infirmary, Manchester, and Department of Histochemistry, Royal Postgraduate Medical School, London*) A number of different methods have been used to stimulate serum gastrin concentration in chronic peptic ulcer disease[1,2]. Oxo tests were performed on two separate occasions in 15 patients to study the reproducibility of the method. There was a highly significant correlation between the integrated gastrin response (IGR), fasting gastrin concentration (FGC) and peak gastrin concentration (PGC).

Twenty-nine patients with recurrent peptic ulceration after previous gastric surgery were investigated using this test. Antral biopsies were obtained from these patients before or at re-operation and the distribution of the antral gastrin cells in these specimens was studied[2]. Seven patients had gastrinomas, the FGC was 1793 ± 468 pg/ml (mean ± SE); in these subjects the serum gastrin concentration did not change during the Oxo test. Eleven patients had an FGC of 150 ± 16 pg/ml, PGC of 306 ± 41 pg/ml, and an IGR of 499 ± 103 pg. The antral biopsies of these patients and those with gastrinomas had not more than one gastrin cell per gland. Eleven other patients had an FGC of 422 to 32 pg/ml, a PGC of 1340 ± 119 pg/ml, and an IGR of 3251 ± 772 pg; the antral biopsies of these patients had 3-8 gastrin cells per gland. The FGC, PGC and IGR of these groups were significantly different. There was no significant correlation between FGC and BAO_{PG}, PGC and PAO_{PG} and IGR and MAO_{PG}. The Oxo test was found to be a simple and useful test in the differential diagnosis of different types of recurrent peptic ulceration.

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Fluid secretion in duodenum and intestinal handling of water and electrolytes in three cases of the Zollinger-Ellison syndrome

J. C. RAMBAUD, R. MODIGLIANI, C. MATUCHANSKY, AND J. J. BERNIER (*Research Group on Physiopathology of Digestion, INSERM U* **54**, *Hôpital Saint-Lazare, 107 rue du Faubourg Saint-Denis, Paris, France*) The slow marker perfusion technique[1] was used in three Zollinger-Ellison (ZES) patients in order to determine basal and postcibal flow rates and compositions of fluids passing the duodenojejunal junction and distal ileum. These measurements, together with a gastric secretion study and faecal collection, gave an assessment of handling of water and ions in the duodenum, small and large intestines. The 24-hour output at the ligament of Treitz was markedly increased (patient 1, 24·7; patient 2, 16·2; patient 3, 14·7); mean 24-hour faecal water outputs were 0·35, 0·10 and 0·21 respectively, indicating an overall intestinal re-absorption higher than 98·5%. In patients 2 and 3, measurement of 24-hour ileal flow rate (6·0 and 4·3) showed that the small intestine reabsorbed 73 and 59% respectively of the fluid leaving the duodenum.

Furthermore, the fasting flow rate and composition of fluid at the duodenojejunal junction were measured during a two-hour basal period followed by a two-hour continuous gastric aspiration period. Removal of gastric secretion (6·6, 4·5 and 3·3 ml per min for patients 1, 2 and 3 respectively) had the following effects on fluid passing at the ligament of Treitz: (*a*) dramatic decrease of flow rate (from 21·8, 13·7 and 10·1 to 6·1, 1·7 and 3·2 ml per min respectively), indicating that the entry of gastric juice induced a considerable fluid secretion into the duodenum; (*b*) increase of osmolality (from 189, 189 and 258 to 261, 289 and 293 mOsm per kg); rise of pH (from 3·5, 2·6, and 4·8 to 7·7, 7·8 and 7·4), and, in patients 2 and 3, a decrease of pCO_2 (from 341 and 215 to 62 and 44 mm Hg) suggesting neutralization of gastric acid by bicarbonate secreted into the duodenum. Conceivably, hypotonicity of proximal luminal fluid may have enhanced its subsequent reabsorption. In conclusion, there is in ZES a considerable increase in the enterosystemic cycle of fluid and ions, a finding which is not reflected by the daily stool weight of these patients.

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Serum alphafetoprotein levels in liver disease: Relation to hepatocellular regeneration and development of hepatoma

N. ELEFTHERIOU, H. THOMAS, J. HEATHCOTE, AND S. SHERLOCK (*Department of Medicine, Royal Free Hospital, Pond Street, London*) Using radioimmunoassay, serial specimens from 32 patients with acute (type A and B) hepatitis and two with paracetamol-induced hepatitis showed elevations of serum alphafetoprotein (αfp) when the transaminases were falling. Alphafetroprotein remained high and fluctuating during a five-month follow up of a patient with 'bridging' necrosis and persistently high transaminases, and was normal in three patients with fulminant hepatitis, three, four and seven days after onset of jaundice. Fifteen of 17 patients with primary liver cell cancer (PLCC) showed high levels of αfp, four were HB_sAg positive. Ten of 51 patients with chronic active hepatitis had raised αfp levels. Three and five months later two of these patients developed clinical PLCC with high αfp levels.

Thirty-nine patients with alcoholic liver disease, 38 with primary biliary cirrhosis, 10 with cryptogenic cirrhosis and 35 with miscellaneous liver diseases gave normal levels (< 20 ng/ml).

CONCLUSIONS

Rising αfp in viral and drug-induced hepatitis reflects hepatocyte regeneration. The failure of αfp to rise in fulminant hepatitis may indicate failure of regeneration or merely reflect the short-time course of the patient's illness.

Serial αfp estimations in chronic active hepatitis are useful in the early diagnosis of primary liver cancer. Patients with levels increasing above 50 ng/ml are at high risk of developing cancer.

Transient lymphocyte-mediated hepatotoxicity in acute viral hepatitis

A. MOUSSOUROS, A. M. G. COCHRANE, A. D. THOMSON, A. L. W. F. EDDLESTON, AND ROGER WILLIAMS (*The Liver Unit, King's College Hospital, London*) An autoimmune reaction directed against a liver-specific membrane lipoprotein is thought to be important in the pathogenesis of active chronic hepatitis, and it has been postulated that an acute hepatitis-B infection may initiate such a reaction. In the present study we have looked for lymphocyte-mediated hepatocyte killing, using a microplate assay technique, in 30 patients with acute viral hepatitis. Of the 14 patients tested within three weeks of the onset of their symptoms significant cytotoxicity was seen in 12 (86%) but it was present in only seven (44%) of 16 tested

after this time.

Cytotoxicity was commoner in the HBsAg-positive cases, being present in 10 (91%) of the 11 compared with nine (47%) of the 19 who were HBsAg negative. This difference was particularly striking in patients studied later in their disease, cytotoxicity occurring in 86% of the HBsAg-positive but in only 11% of the negative cases.

These results suggest that, in addition to the known immunological reactions against viral antigens, an autoimmune reaction directed against liver specific protein also occurs during the acute phase of viral hepatitis. In the majority of cases this reaction is probably transitory although the higher incidence of cytotoxicity in HBsAg-positive cases would be in keeping with the increased incidence of chronic liver disease following hepatitis B virus infection.

The effect of lymphocytic transfer factor on hepatitis B surface antigen-positive chronic liver disease

STEPHAN JAIN, H. C. THOMAS, AND SHEILA SHERLOCK (*Departments of Medicine and Infectious Diseases, Royal Free Hospital, Pond Street, London, and Coppetts Wood Hospital, London*) Cell-mediated immunity may be defective in hepatitis B antigen (HbsAg)-positive chronic liver disease. Lymphocytic transfer factor (TF) is known to stimulate such immunity and might, therefore, be of therapeutic benefit. Lawrence's method has been used to prepare 'normal' TF from healthy HbsAg-negative blood donors and 'specific' TF from subjects recently recovered from HbsAg-positive hepatitis who have cleared the antigen from the blood. Three patients have been treated. One patient with HbsAg-positive chronic active hepatitis and cirrhosis showed no response to 'normal' TF but 'specific' TF increased the T lymphocytes (measured by a rosetting technique) from 300 to 600/μl: a second similar patient also showed no response to 'normal' TF but 'specific' TF increased the serum aspartate transaminase values transiently suggesting stimulation of cell-mediated immunity with a resulting hepatitic reaction. The third patient suffered from HbsAg-positive active chronic hepatitis complicated by primary liver cancer; he was receiving corticosteroid therapy, and showed no response to either 'normal' or 'specific' TF. In all three patients titres of serum HbsAg did not change.

CONCLUSION

'Specific' transfer factor has been prepared from patients recovered from hepatitis B. Three patients have been treated and in two an effect was shown on T lymphocytes or on liver function. Further trials of this treatment seem justified.

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Primary and secondary immune responses to ϕX 174 in patients with primary biliary cirrhosis and chronic active hepatitis

H. C. THOMAS, R. HOLDEN, J. VERRIER-JONES, AND D. PEACOCK (*Department of Immunology, Glasgow University, and Department of Medicine and Bacteriology, Bristol University*) Patients with primary biliary cirrhosis (PBC) and chronic active hepatitis (CAH) develop hyperglobulinaemia. It is suggested that this might be due either to increased antigenic challenge or increased reactivity of the lymphoid organs to normal amounts of antigen. We have immunized patients intravenously with the bacteriophage ϕX 174 and measured the primary and secondary antibody responses. Patients with PBC have significantly higher serum IgM concentrations than either normal individuals or patients with other forms of liver disease. We have therefore analysed the 19S and 7S components of the response in these patients.

Because the response to this antigen is thymus dependent we have measured T cell and also B cell concentrations in the peripheral blood of these patients using rosetting techniques.

Primary responses were normal in 11 patients with PBC and four patients with HB/Ag-negative CAH. Secondary responses were grossly impaired in both disease groups. Antibody at the peak of the secondary response was separated into 19S and 7S on a sucrose gradient. In patients with impaired total antibody response there was evidence of defective switching from 19S to 7S antibody production. This was true of the patients with PBC and CAH and did not correlate with the patterns of serum immunoglobulins. The degree of impairment of switching was inversely related to peripheral blood T cell concentrations.

These results demonstrate that the hyperglobulinaemia of PBC and CAH is not associated with a general enhancement of antibody production. On the contrary the response to thymus-dependent antigens was markedly depressed. The 19S response was within the normal range and the defect is mainly in conversion to a 7S response.

Progression of histological changes in hepatitis B antigen carriers

E. TAPP, D. HOLLANDERS, AND I. W. DYMOCK (*Departments of Pathology and Medicine, University Hospital of South Manchester*) In earlier reports on the histological appearances of the liver in asymptomatic HB_sAg-positive blood donors we have recorded a wide range of abnormalities including focal parenchymal necrosis, chronic persistent hepatitis, chronic aggressive hepatitis and cirrhosis. Twenty of these carriers, who have been followed for periods of between two and four years, have had serial liver biopsies and regular biochemical tests of liver function. All have remained HB_sAg-positive.

During the period of study eight of the 20 carriers have shown progression of the histological changes.

Of five with a chronic aggressive hepatitis at the first biopsy, two have progressed to a cirrhosis with some reduction in the inflammatory cell infiltrate. One other carrier with a chronic aggressive hepatitis initially showed more marked inflammatory features two years later.

Two of eight carriers with a chronic persistent hepatitis at the first examination have progressed to a chronic aggressive hepatitis. Four others are unchanged and a further two have some reduction of the inflammatory cell infiltrate in the portal tract. Three of the five carriers with focal parenchymal lesions have developed features of a chronic persistent hepatitis on follow up. Although serial liver function tests were sometimes abnormal only in those with an aggressive hepatitis was this a constant feature.

From this study we postulate that in asymptomatic HB/Ag carriers the histological abnormalities may progress with the eventual development of a cirrhosis.

Effect of somatostatin on pancreatic and biliary function

S. R. BLOOM, S. N. JOFFE, AND J. M. POLAK (*Departments of Medicine, Surgery and Histochemistry, The Royal Postgraduate Medical School, Hammersmith Hospital, London*) Somatostatin has recently been shown by radioimmunoassay to occur in normal pancreas and gastric and upper

small intestinal mucosa[1] and was subsequently found to be produced by the D cell[2]. It is thus of considerable interest to ascertain its spectrum of actions on the alimentary tract. Four pigs were studied under anaesthesia during a 60-minute intraduodenal administration of fat. Marked gall-bladder contraction was seen in all pigs by five minutes and increased further until a 10-minute somatostatin infusion (0·4 μg/kg/min) was commenced at 30 minutes. Mean gallbladder pressure fell from 13·5 ± 1·2 (SE) cm H_2O immediately prior to somatostatin to a nadir of 3·5 ± 1·5 cm H_2O ($P < 0·01$) and rose to 10·0 ± 1·9 cm H_2O by the end of I D fat infusion 20 minutes later. An equally dramatic gallbladder inhibition was seen when somatostatin was administered during infusion of exogenous cholecystokinin-pancreozymin (0·03 I D U/kg/min) as previously shown[3]. No effect of somatostatin was seen on pancreatic bicarbonate juice flow stimulated by intraduodenal HCl (0·45 mmoles/kg/min) or exogenous secretin infusion (0·03 CU/kg/min).

Somatostatin is thus a selective inhibitory hormone acting in the gut on the target tissues of the gastrin and cholecystokinin-pancreozymin group of hormones.

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[1]Arimura, A., Sato, H., Du Pont, A., Nishi, N., and Schally, A. V. (1975). Abundancy of immunoreactive GH release inhibiting hormone in the stomach and pancreas of rat. *Fed. Proc.*, **34**, 273.

[2]Polak, J. M., Pearse, A. G. E., Grimelius, L., Bloom, S. R., and Arimura, A. (1975). Growth hormone release inhibiting hormone in gastrointestinal and pancreatic D cells. *Lancet*, **1**, 1220-1222.

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Bicarbonate and cyclic AMP secretion in pure pancreatic juice: dose-response curves to synthetic secretin in man

S. DOMSCHKE, W. DOMSCHKE, W. RÖSCH, S. J. KONTUREK, E. WÜNSCH, AND L. DEMLING (*Department of Medicine, University of Erlangen-Nürnberg, D-852 Erlangen, W. Germany*) In seven volunteers, pure pancreatic juice was obtained by endoscopic cannulation of the papilla of Vater[1]. The subjects had a normal retrograde pancreatogram, and received no premedication. Via an additional tube, gastric contents were continuously aspirated. Synthetic secretin was intravenously infused in doses doubling every 20 min. Volume of pancreatic juice was proportional to the log of the secretin dose. A significant rise ($P < 0·05$) in pancreatic juice flow was already elicited at a dose of 0·031 clinical units-CU-/kg. hr (corresponding to 8·05 ng/kg. hr). Maximum flow rate approximating 250 μl/5 min. kg b.w. was attained during infusion of 0·5 CU/kg. hr. μ-equiv. At the same dose maximal bicarbonate outputs averaging 374 μ-equiv/hr. kg bw were achieved, whereas bicarbonate ion concentration approached peak values (135 ± 9 μ-equiv/ml) even during 0·125 CU/kg. hr. Bicarbonate concentrations showed a tendency to fall at supramaximal doses. Protein concentrations decreased due to graded doses of secretin with protein outputs remaining constant. The effect of increasing secretin doses on bicarbonate and cyclic AMP concentrations was remarkably similar ($rS = 0·635$, $P < 0·001$). Since in dog experiments[2] both cyclic AMP and bicarbonate outputs in pancreatic juice were significantly correlated with cyclic AMP tissue concentrations, a participation of cyclic AMP in human pancreatic bicarbonate secretion may also be suggested.

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Pancreatic D cells in normal and pathological human pancreas

JULIA M. POLAK, S. R. BLOOM, A. ARIMURA, AND A. G. E. PEARSE (*Departments of Histochemistry and Medicine, The Royal Postgraduate School, Hammersmith Hospital, London, and Veterans' Administration Hospital, New Orleans, USA*) Somatostatin (growth hormone release-inhibiting-hormone) has been found in stomach, pancreas and upper small intestine by radioimmunoassay[1]. The amount found in the pancreas was comparable to that found in the arcuate nucleus of the hypothalamus. By using combined immunocytochemical and histological methods for secretory granules the D cell of the gut and pancreas has been demonstrated as the origin of this hypothalamic peptide. The powerful local actions of somatostatin on the alimentary tract may therefore be considered as potentially physiological.

The pancreases from 15 patients suffering from a variety of abnormalities, mainly endocrine tumours, have been investigated using a range of histological stains for D cells as well as immunocytochemical and ultrastructural methods. Those cases which had islet cell hyperplasia (nesidioblastosis, islet hyperplasia associated with the Z-E syndrome and pseudo-Verner-Morrison syndrome) also had a concomitant D cell hyperplasia demonstrated by all the methods employed. The most striking increase was found in the normal pancreas alongside VIP-producing tumours (Verner-Morrison syndrome) and also in the severe watery diarrhoea situation unassociated with a pancreatic tumour (pseudo-Verner-Morrison syndrome). In these situations the D cells were extremely numerous and were brightly fluorescent.

This is the first information on pathological changes in the recently delineated pancreatic somatostatin.

Reference

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Effects of cholecystokinin, secretin and acetylcholine on pancreatic enzyme secretion and tissue levels of cyclic GMP and cyclic AMP

R. F. HARVEY, JANET ALBANO, K. D. BHOOLA, AND A. E. READ (*Departments of Medicine and Pharmacology, University of Bristol*) The mechanisms of action on pancreatic cells of the various stimuli of pancreatic exocrine secretion are poorly understood. Secretin-induced water and electrolyte secretion is probably brought about by intracellular formation of cyclic adenosine monophosphate (cAMP)[1], and cAMP has also been suggested as a mediator of enzyme secretion. However, the rat pancreas *in vivo* was recently reported to show no increase in cAMP levels after cholecystokinin - pancreozymin (CCK), whereas cyclic guanosine monophosphate (cGMP) rose to twice the fasting level[2], suggesting a possible role for cGMP in enzyme secretion.

We have therefore studied the effect of CCK, secretin and acetylcholine on pan-

creatic cAMP and cGMP levels and enzyme secretion using incubated guinea pig pancreatic slices. In contrast to secretin (1×10^{-7}M), neither CCK (GIH batch 273121, 10^{-7}M) nor acetylcholine (10^{-6}M-10^{-3}M) produced any elevation in pancreatic cAMP. Secretin did not increase cGMP levels, but both CCK (5×10^{-9}M-1×10^{-7}M) and acetylcholine triggered a very rapid increase in cGMP, beginning within 5 to 30 seconds of the stimulus, showing a peak five- to nine-fold increment after about two minutes and falling rapidly thereafter. Enzyme secretion began soon after, a significant increase being seen at five minutes. Similar responses were seen with highly purified CCK (batch of 11.11.1970, specific activity about 3 Ivy units/μg, courtesy of Professor V. Mutt), and synthetic CCK-octapeptide (courtesy of Dr M. Ondetti), indicating that the observed effects were not due to contaminants in the GIH CCK preparation.

We conclude that pancreatic enzyme secretion in response to CCK or acetylcholine may be triggered by a rise in intracellular cGMP.

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Studies on the mechanism of fat absorption in congenital isolated lipase deficiency

D. P. R. MULLER, J. P. K. MCCOLLUM, R. S. TROMPETER, AND J. T. HARRIES (*Institute of Child Health and The Hospital for Sick Children, Great Ormond Street, London*) Studies in a patient with congenital isolated lipase deficiency are reported. Diagnosis was established by analysis of duodenal contents following a standardized test meal. Pancreatic lipase was undetectable on two separate occasions whereas other pancreatic enzyme activities were normal, ie, trypsin, amylase and esterase, and total and individual bile salt concentrations were also normal. Colipase was present (Professor Borgström, Lund).

Despite complete absence of pancreatic lipase more than 50% of dietary fat was absorbed. Studies to elucidate the mechanism of fat absorption were performed and the following observations were made:

1 Hydrolysis of dietary triglyceride was demonstrated in gastric and duodenal contents.

2 Lipolytic activity was present in gastric contents but was absent in saliva.

3 Triglyceride was present in the micellar phase of duodenal contents providing an appropriate physicochemical substrate form for hydrolysis by pancreatic esterase.

4 *In-vitro* animal experiments suggested that absorption of intact triglyceride is an unlikely explanation for the absorption of fat.

These observations suggest that in the absence of pancreatic lipase, gastric lipase and pancreatic esterase may play an important compensatory role in the absorption of dietary fat.

Disturbed brain tryptophan metabolism in fulminant hepatic failure

C. O. RECORD, R. A. CHASE, I. M. MURRAY-LYON, G. CURZON, AND ROGER WILLIAMS (*The Liver Unit, King's College Hospital Medical School, London, and the Department of Neurochemistry, Institute of Neurology, London*) A disturbance in serotonin metabolism may be important in hepatic encephalopathy and increased concentrations in brain are associated with sleep. The synthesis of serotonin in brain is influenced by changes in the concentration of the precursor amino acid tryptophan and we have therefore determined its concentration in the brain and plasma of patients dying of fulminant hepatic failure (FHF).

Brain tryptophan concentrations were increased fourfold ($0{\cdot}14 \pm$ SE $0{\cdot}02$; $n = 13$ compared with $0{\cdot}04 \pm 0{\cdot}008$ μ mol/g, $n = 5$; $P < 0{\cdot}025$) and this was associated with a fivefold increase in plasma free tryptophan (22 ± 3, $n = 28$ compared with $4 \pm 0{\cdot}5$ μ mol/l, $n = 10$; $P < 0{\cdot}005$). 5-Hydroxyindoleacetic acid, a degradation product of serotonin, was also significantly increased ($0{\cdot}58 \pm 0{\cdot}06$ compared with $0{\cdot}30 \pm 0{\cdot}05$ μg/g; $P < 0{\cdot}025$) in the brain suggesting an increase in brain serotonin turnover.

Brain tryptophan concentration may also be influenced by the concentrations in plasma of the branched chain and other neutral amino acids which compete with tryptophan for uptake into the brain. This mechanism may be important in cirrhosis when plasma branched chain amino acids are decreased. In patients with FHF, however, the concentrations in plasma were normal and it is of interest that in those patients who died, brain valine ($P < 0{\cdot}05$) and isoleucine ($P < 0{\cdot}05$) were significantly increased. It is concluded that branched chain amino acids are unlikely to influence brain tryptophan in FHF. Whether administration of these amino acids in order to decrease brain tryptophan, as recently proposed[1], will be beneficial, remains to be investigated.

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Liver function tests and histology in survivors of acute paracetamol (Acetaminophen) poisoning

A. N. HAMLYN, O. F. W. JAMES, M. LESNA, S. H. ROBERTS, A. J. WATSON, AND ADRIAN P. DOUGLAS (*Gastroenterology Group and Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne*) Twenty-four consecutive survivors of acute paracetamol overdosage were studied on admission to hospital and three months later. There were 18 females and five males; ages ranged from 13 to 65 years. Amounts of paracetamol taken varied from 5 to 50 grams and four-hour interpolated blood levels from 9 to 290 μg ml^{-1}. Six cases where levels exceeded 170 μg ml^{-1} received cysteamine. All patients had standard biochemical investigation and a liver biopsy when first seen and at three months. Three patients developed severe liver damage as judged on biochemical and histological evidence. Five patients developed moderate damage and 16 mild or minimal damage.

At three months follow up no patient had clinical signs of liver disease. Prothrombin time, serum bilirubin, alkaline phosphatase and aspartate transaminase had returned to normal in every case. Histology of liver tissue obtained by needle biopsy showed in all patients an increase of lipofuscin in centrilobular hepatocytes. In some cases there were groups of enlarged Küpfer cells containing diastase-resistant, PAS-positive material in the centrilobular area. Practically all cases demonstrated focal condensation of reticulin. One case, the most severely affected originally, still showed increased collagen in the centrilobular sinusoids.

Cysteamine therapy does not appear to modify liver function or histological appearances at three months.

We conclude that in survivors of paracetamol overdosage, practically complete recovery of hepatic function and structure is the rule, even in those intially severely affected.

Controlled trial of cysteamine and dimercaprol in the prevention of liver damage after paracetamol overdose

B. G. GAZZARD, R. D. HUGHES, A. D. CHHIBBER, J. R. BENNETT, I. M. MURRAY-LYON, BETTINA DORDONI, AND ROGER WILLIAMS (*The Liver Unit, King's College Hospital, London, Princess Elizabeth Hospital, Harlow, and the Hull Royal Infirmary, Hull*) Liver damage following paracetamol overdose results from excessive quantities of the drug being metabolized via a chemically reactive derivative which depletes hepatocellular reduced glutathione and binds to liver cell proteins. Recently, Prescott *et al*[1] have reported in an uncontrolled clinical trial that administration of cysteamine, a sulphydryl group donor which substitutes for reduced glutathione, exerts a protective effect. However, cysteamine has unpleasant side effects, and has to be specially made up for each patient.

We have therefore carried out a controlled trial of dimercaprol, another sulphydryl group donor (42 mg/kg over 48 hours) in comparison with cysteamine (3·2 g intravenously over 20 hours). Both were given within 12 hours of overdose to patients who had high plasma paracetamol levels and were at risk from liver damage. Analysis of the changes in liver function over the three days after admission showed that four of the 10 patients receiving dimercaprol developed a serum total bilirubin level greater than 90 mmol/l and a serum aspartate aminotransferase of over 1000 iu/l compared with two of the 10 given cysteamine. However, five of the six patients showing these changes were treated more than six hours after ingestion of the tablets, suggesting that the severity of liver damage was related more to the interval between overdose than to the agent used.

In practice, dimercaprol was more convenient to use, side effects being restricted to severe abdominal cramps in four cases, whereas all patients receiving cysteamine became severely nauseated, and one developed meningism.

Reference

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Screening vinyl chloride monomer workers for liver disease[1]

D. M. J. WILLIAMS, K. J. W. TAYLOR, I. R. CROSSLEY, AND P. M. SMITH (*BP Chemicals International Ltd., Barry, The Royal Marsden Hospital, Sutton, and Department of Medicine, Llandough Hospital, Penarth*) A suvery of workers to determine whether changes had been induced by past exposure to vinyl chloride was carried out by means of a clinical examination and standard haematology and liver function tests.

Of 487 workers examined, 102 (20·9%) had abnormalities on initial testing, but only two were finally shown to have portal hypertension. Both had been first identified through thrombocytopenia, having normal liver function tests. The remainder were either normal on repeat testing or had minor changes attributable to alcohol (10 cases) or Gilbert's disease (six cases). In comparison, 44 (23%) of 112 control subjects had initial test abnormalities.

A test sample of 19 workers was therefore chosen at random and examined blind by Grey scale ultrasonography. Four with minimal or no exposure were confirmed as normal, but 11 of the remainder had abnormalities consisting of an enlarged portal vein in seven, splenomegaly in eight and changes in hepatic texture in seven. Six of these 11 workers had previously been considered entirely normal.

We concluded that Grey scale ultrasonography had distinct advantages over standard methods for screening workers exposed to vinyl chloride monomer.

The effects of various anaesthetics and abdominal surgery on liver blood flow in man

R. E. COWAN, B. T. JACKSON, AND R. P. H. THOMPSON (*Gastrointestinal Laboratory, St. Thomas' Hospital, London*) The mechanism of any association between halothane and postoperative liver dysfunction is uncertain, but reduction in liver blood flow during anaesthesia and surgery may be important.

To assess this the peripheral disappearance rate of indocyanine green (ICG, 0·25 mg/kg body weight) was measured in 23 adult anaesthetized with halothane (9), trilene (8), and droperidol and fentanyl (6). The ICG half-life times before anaesthesia, after induction, during abdominal surgery and two hours after surgery were 3·9 ± 1·2 (mean ± SD), 5·5 ± 2·2 (41% increase, $P < 0.005$), 4·0 ± 0·9 and 4·3 ± 1·8 min respectively. Assuming constant blood volume and hepatic extraction efficiency, mean liver flow was therefore reduced by 23% (range + 285 to − 1140 ml/min) after induction. This change was greatest with trilene, while with halothane the $T_{\frac{1}{2}}$ increased from 3·9 ± 1·5 to 4·9 ± 1·75 min (NS), compared with 3·9 ± 1·1 to 5·3 ± 2·4 min ($P < 0.05$) with both non-halothane anaesthetics.

In 10 of these patients liver blood flows were also estimated from ICG extraction using hepatic vein catheterization. Results were similar: blood flows 1389 ± 450 937 ± 507 (32% decrease, range + 649 to − 1004 ml/min, $P < 0.05$), 1404 ± 593 and 1270 ± 451 ml/min respectively.

These results demonstrate a marked reduction in liver blood flow after anaesthetic induction, with recovery during abdominal surgery, and suggest that halothane has no greater adverse effect on liver function by this mechanism.

Hepatic enzyme changes in alcoholic liver disease[1]

CAROL A. SEYMOUR, G. NEALE, AND T. J. PETERS (*Department of Medicine, Royal Postgraduate Medical School, London*) Serum 5'nucleotidase, alkaline phosphatase, leucyl-β-naphthylamidase and γ-glutamyl transpeptidase are commonly assayed in the clinical assessment of patients with suspected liver disease. Raised levels of these enzymes in combination with a high ethanol intake are often an indication for liver biopsy. The biochemical nature of the tissue damage in alcoholic liver disease is unknown and in addition there are patients with raised serum enzyme levels but with normal hepatic histology. A study was therefore undertaken of the activities of plasma membrane, lysosomal and microsomal enzymes in closed needle biopsy specimens from 62 patients with suspected alcoholic liver disease. The following histological categories were used: normal histology, fatty change, alcoholic hepatitis, cirrhosis and cirrhosis with siderosis. Enzymes were assayed with micro techniques[2] in both serum and tissue and the levels were compared with those in control subjects (normal liver histology and serum liver function tests).

In all groups of alcoholic patients, including those with histologically normal livers, the plasma membrane enzymes (alkaline phosphatase, leucyl-β-naphthylamidase, γ-glutamyl transpeptidase) were elevated two to four-fold. 5'Nucleotidase, selectively localized to the plasma membrane, showed a 10 to 20-fold increase in activity. There was no correlation between degree of hepatic damage and enzyme

levels, although the patients with cirrhosis tended to have higher levels than those with fatty change. When all categories were combined statistically significant positive correlation coefficients were obtained for the plasma membrane enzymes between serum and liver tissue. Enzymes associated with the microsomes (neutral α-glucosidase) and with lysosomes (N-acetyl-β-glucosaminidase, acid phosphatase, β-glucoronidase) showed little or no difference between the different histological groups. Assessment of lysosomal integrity (latent and sedimentable N-acetyl-β-glucosaminidase)[3] also showed that the properties of this organelle are normal in liver from patients with alcoholic liver disease suggesting that lysosomes are not implicated in the pathogenesis of the liver damage.

It is concluded that ethanol has a selective effect on the plasma membrane of the liver cells but this action is probably not directly implicated in the pathogenesis of the hepatic damage.

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Vasoactive intestinal peptide characteristics in human gut

J. M. POLAK, A. G. E. PEARSE, AND S. R. BLOOM (*Departments of Histochemistry and Medicine, The Royal Postgradutae Medical School, Hammersmith Hospital, London*)

The cell origin of the new hormone, vasoactive intestinal peptide (VIP), has recently been localized by immunohistochemistry[1]. In order to integrate such light microscopy studies with ultrastructural analysis a new technique has been developed. Numerous pieces of fresh human gastrointestinal mucosa were fixed in p-benzoquinone[2] and resin-embedded blocks prepared. Alternate thick (1 μ) sections were stained by immunofluorescence and thin sections with conventional electron microscopy stains. By alignment of geographical land marks present in the sections prepared alternatively for light microscopy and electron microscopy it was possible to ascertain that (1) VIP cells were present throughout the gastrointestinal tract being particularly numerous in the ileum and colon. (2) VIP cells were localized predominantly in the mid zone of the mucosa whereas, for example, enteroglucagon (EG cells) were found predominantly in the basal parts of the glands. (3) Histological and ultrastructural stainings for secretory granules indicated that VIP cells were only weakly argyrophilic and the granules were of small to medium size and polymorphic.

These new methods presented here are useful in understanding gut endocrinology and the bifunctional reagents used for the VIP cells provide acceptable ultrastructural preservation with a minimum of interference with the immunogenic sites of the hormone.

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Characterization of the new gastrointestinal hormones

M. G. BRYANT AND S. R. BLOOM (*Department of Medicine, The Royal Postgraduate Medical School, Hammersmith Hospital, London*)

Recent advances in gastrointestinal endocrinology have been very rapid with the discovery, isolation and purification of three new hormonal polypeptides—vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP), and motilin. The full characterization of their tissue forms has not, however, been undertaken. This is particularly important in view of the assay problems with more classical hormones brought to light by the discovery of multiple molecular species.

We have studied secretin, VIP, GIP and motilin in crude acid ethanol extracts of primate gut. Individual extracts of different regions of baboon gut were subjected to gel chromatography (Sephadex G50 Superfine) and the hormone content of the eluted fractions was measured by radioimmunoassay. With all four hormones, only a single peak of immunoreactivity was demonstrated. This was equally true with extracts from various anatomical regions of the gastrointestinal tract. The elution characteristics of the primate hormones were also compared with the original pure porcine hormones. No 'big' hormones were demonstrated.

Thus, unlike enteroglucagon and gastrin, there appear to be only single forms of the new hormones VIP, GIP and motilin. These data also provide good evidence for the high degree of specificity of the radioimmunoassays employed.

Is intermittent chenodeoxycholic acid therapy feasible for dissolving gallstones? The speed of change in biliary lipids and bile acids after starting and stopping treatment

JOHN H. ISER, GERARD M. MURPHY, AND R. HERMON DOWLING (*Gastroenterology Unit, Department of Medicine, Guy's Hospital and Medical School, London*)

For chenodeoxycholic acid (CDCA) to dissolve gallstones, bile must become unsaturated with cholesterol[1], but it is not known how quickly representative changes in bile lipids develop, nor for how long bile remains unsaturated on withdrawing therapy. We therefore measured biliary cholesterol saturation indices (SI)[2] and related them to bile acid composition at frequent intervals in fasting gallbladder bile from seven gallstone patients after starting, and from six after stopping, treatment with 12-17 mg CDCA.kg^{-1} day^{-1}.

RESULTS

After starting, SI fell from 1·63 ± SEM 0·16 to 1·17 ± 0·13, 1·09 ± 0·11, 1·03 ± 0·11, 1·01 ± 0·13, 0·94 ± 0·03 and 0·87 ± 0·06 at days 4, 7, 14, 21, 28 and 49 respectively. The proportion of CDCA in the bile acid pool increased from 24 ± 3·5% to 64 ± 6·5% in two days and 81% within six weeks, the reduction in SI correlating with the percentage of CDCA ($r = 0·83$; $P < 0·001$).

When treatment stopped, SI increased from 0·78 ± 0·12 to 1·09 ± 0·15 within three weeks. There was again a reciprocal, but not significant, fall in the percentage of CDCA.

SUMMARY

After starting CDCA, bile lipids do not show representative changes before one month, the change in SI correlating with the percentage of CDCA. On withdrawing treatment, bile remains unsaturated for only three weeks, suggesting that continuous CDCA is necessary to maintain an unsaturated bile.

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Gram stain on bile aspirated at operation: A rational approach to antibiotic therapy in biliary disease

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Biliary microorganisms are responsible for complications such as wound sepsis and septicaemia following operations on the biliary tract[1] and even endotoxic shock after transhepatic cholangiography and endoscopic retrograde choledochopancreatography (ERCP)[2]. Organisms are isolated from bile in only 30% of patients with biliary disease and in surgical practice antibiotics have been shown to be justified only if organisms are found in the bile at operation[3].

The aim of this study has been to determine the accuracy of Gram stain on uncentrifuged bile as an aid to the choice of antibiotic cover and as a means of avoiding indiscriminant prophylaxis.

Gram stains on 100 operative bile samples by routine laboratory staff indicated a diagnostic accuracy of 76% (13% false positive, 7% false negative and 4% wrong organism). In the hands of an experienced microbiologist the accuracy in 55 further patients was 87% (only 2% false positives). Results showed that 92% of Gram-positive organisms (mainly *Streptococcus faecalis* and *Clostridium welchii*) were sensitive to ampicillin and all Gram-negative bacteria were sensitive to gentamicin. When peroperative antibiotics were administered according to the results of Gram stain on bile (90 patients) and compared with controls receiving no antibiotic (104 patients) wound sepsis was reduced from 18% to 7% ($P < 0.05$) and bacteraemia from 10% to 1% ($P < 0.05$).

These data indicate that immediate Gram stain on bile will indicate appropriate antibiotic cover for patients requiring operation or radiological procedures on the biliary tract.

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Intravenous cholangiography, is technique important?

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Over the last 10 years a considerable amount of conflicting data has accumulated concerning the dose and optimal rate at which Iodipamide and more recently Ioglycamide should be administered intravenously in order to (a) produce maximum radiographic opacification of the biliary tree and (b) reduce toxic side effects to a minimum.

We have conducted a survey of the exact method used for performing intravenous cholangiography in 100 randomly selected radiology departments, throughout the UK. There was considerable variation in the rate of administration of the radio-contrast agents ranging from 4000 mg min^{-1} for five minutes to less than 60 mg min^{-1} for five hours.

Since it was unlikely that such a vast range of dose regimes should be equally effective and safe (the mortality of the investigation being 1 in 5000 examinations[1]) we decided to conduct our own trial. We have measured the plasma concentration[2] and biliary excretion of Iodipamide and Ioglycamide following both single bolus injection and one-hour drip infusion techniques at rates varying from 1 to four mg kg^{-1} min^{-1}. At the same time the resulting radiological opacification of the common bile duct has been critically assessed by two radiologists.

Preliminary results suggest that the method of administration of intravenous biliary contrast media used in many hospitals is less than optimal and could prove hazardous.

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Management of suspected extrahepatic biliary atresia

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Recent reports[1,2] emphasize that if surgical correction of extrahepatic biliary atresia (EHBA) is to be successful this must be carried out within the first 10 weeks of life. However at this time, differential diagnosis from the various causes of the neonatal hepatitis syndrome is particularly difficult. To determine which clinical, laboratory and pathological findings were of most help in diagnosis, we have analysed such data from 34 infants with EHBA and 103 with neonatal hepatitis (NH).

The results show that whereas all infants with EHBA weighed 2·5 kg and were born after normal full-term pregnancies, 35 of those with NH had birth weights of less than 2·5 kg and 18% were born prematurely. Although splenomegaly and hepatomegaly of greater than 5 cm was more common in EHBA, clinical findings were of little help, and standard liver function tests of no value in distinguishing the two conditions. Crucial investigations were percutaneous liver biopsy, the appearances being characteristic of EHBA in 17 of the 22 biopsies and of neonatal hepatitis in 76 of the 82 biopsies from patients with NH. The Rose Bengal faecal excretion test was also helpful being less than 10% in 27 of 29 infants with EHBA as compared with only three of 20 infants with NH. When biopsy findings and the Rose-Bengal test are considered together, biliary obstruction was correctly identified preoperatively in all instances, and none of the cases of neonatal hepatitis were subjected to an unnecessary laparotomy. However, in only four infants was the diagnosis made and the patient operated on within the first 10 weeks. One of these now has good bile drainage. The 30 having a laparotomy at an older age are all either developing cirrhosis or have died.

Thus accurate distinction is possible at this early stage, and it is vital that possible cases are referred earlier and much before the usually recommended time of four months after birth.

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Ultrastructural characteristics of the oesophageal mucosa in man

P. N. DILLY AND C. N. MALLINSON (*Department of Anatomy, University College,*

London, and Greenwich Hospital Gastrointestinal Unit) The object of this study was to correlate surface ultrastructure with underlying architecture in oesophageal mucosa. Biopsies of mucosa were obtained at endoscopy from the lower oesophagus in patients with oesophageal reflux and positive acid-infusion tests and from control subjects. Biopsies were examined by light microscopy and scanning electron microscope (SEM), surface cells were then levered off by microdissection within the SEM. From the same biopsies samples were cut transversely and examined by transmitting electron microscope (TEM). In tissue from normal subjects surface cells under the SEM showed long, fine ridges in whorls. The borders of the cells were closely contiguous and the mucosal surface was smooth. Under the TEM each mucosal cell represented the top of a regular stack of cells showing progressive maturation from the germinal layer upwards. In tissue from patients with heartburn cell surfaces showed less well defined ridges and whorls and the mucosal surface was irregular due to cells at different stages of desquamation. Under the TEM maturation of cells in the stacks was less complete. These findings suggest that changes seen in the surface cells may be mediated in part by an alteration in maturation and not simply to contact with acid.

[1]Shown on video film.

Studies of the oesophageal antireflux mechanism using a modified rapid withdrawal manometric method and combined fluoroscopy

J. LENNON, W. COPELAND, G. LIDGARD, M. EASTWOOD, AND W. SIRCUS (*Gastrointestinal Unit and Department of Radiology, Western General Hospital, Edinburgh*) The stepwise withdrawal method of measuring the pressure within the lower oesophageal sphincter (LOS) frequently produces tracings which because of the superimposition of the effects of swallowing and respiration make interpretation difficult. Techniques of rapid withdrawal eliminate these variables[1].

We describe a modified rapid withdrawal method. Using a recording catheter with two equidistant side orifices, water infused (3·2 ml/min) is withdrawn through the LOS at a fixed rate (0·7 cm/sec). Eight withdrawals are successively obtained with respiration suspended in inspiration and expiration alternately. Pressures are expressed as peak heights and as an index based on the area under the sphincter profiles.

Seventeen controls and 11 patients with reflux oesophagitis were studied. The mean (± SEM) peak sphincter pressure in controls was 37·0 ± 3·6 (mmHg) compared with 20·3 ± 2·5 for refluxing patients ($P < 0.005$). The index of mean sphincter profile area in controls (8·8 ± 1·0) was significantly higher than that of the patients with reflux (4·8 ± 1·3) – $P < 0.01$. Pressure measurements of successive withdrawals showed insignificant variability.

The contribution of the diaphragm to the sphincter profile was evaluated by combining pressure recordings with simultaneous fluoroscopy on videotape. This showed in all subjects that the distal peak of the profile corresponds with the position of the diaphragm. Proximal peaks in controls are usually recorded about 2 cm above the diaphragm, whereas in patients with reflux they correspond with the proximal end of the hernial sac.

Our method produces clearly defined reproducible sphincter profiles, and when utilized in combination with simultaneous fluoroscopy further clarifies the relative contributions of the diaphragm and the LOS to the gastro-oesophageal antireflux mechanism.

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Computer-aided diagnosis of dyspepsia: A prospective series with emphasis upon comparison with endoscopic findings

F. T. DE DOMBAL, JANE C. HORROCKS, W. A. F. MCADAM, A. G. MORGAN, C. PACSOO, AND A. DARNBOROUGH (*Airedale General Hospital, Steeton, Yorkshire, and the University of Leeds*) Recent reports concerning the value of computer-aided diagnosis in patients with dyspepsia have produced somewhat encouraging results[1,2], yet three questions remain. First, can an automated system developed in one geographical area be 'transferred' to another area without loss of accuracy? Second, what agreement is there between computer-aided prediction and endoscopic findings? Third, has an automated system any role in selecting 'high-risk' patients for intensive investigation?

In this study, 104 patients gastroscoped at Airedale District General Hospital were interviewed immediately before endoscopy (by a non-medically-qualified 'physician's assistant'), and the findings analysed via a small computing system using data from 360 patients previously analysed in Leeds. Of the 50 gastric or duodenal lesions seen at endoscopy, 84% were correctly predicted by the computer-aided system (roughly the same accuracy as in Leeds). Eleven of 13 gastric cancers seen were correctly predicted. The computer-aided prediction also matched the endoscopic findings in 11 of 13 patients specially referred with '*x*-ray negative' dyspepsia.

It is suggested (*a*) that a simple automated system can be transposed geographically without loss of accuracy, and (*b*) where endoscopic facilities are not readily available, this type of analysis, using simple equipment, may be one means of selecting 'high-risk' patients for intensive investigation.

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Is long-term prophylaxis for recurrent gastric ulceration a practical proposition?

G. GREEN, D. HOLLANDERS, B. E. BOYES, I. L. WOOLF, D. J. COWLEY, AND I. W. DYMOCK (*Departments of Medicine and Surgery, University Hospital of South Manchester*) Although medical treatment can usually produce healing of a gastric ulcer a proportion eventually recur. As these recurrent ulcers may be associated with complications we felt it important to assess the feasibility of long-term prophylaxis of recently healed gastric ulcers with a view to preventing or reducing the incidence of recurrence.

Forty-one patients with known gastric ulceration which had been confirmed as healed on both endoscopy and barium meal examination within the previous month were included in the study. Treatment was given on a double-blind basis with either a placebo or deglycyrrhizinized liquorice (Ulcedal) in the usual therapeutic dose. Each patient was seen and assessed at monthly intervals and endoscopy and barium meal examinations were repeated every six months or sooner if symptoms recurred. The patients continued on treatment indefinitely until there was evidence of recurrent ulceration.

Only eight of the 41 patients failed to

continue in the study. Five of these withdrew for personal reasons within the first month. One other withdrew at one year and two were withdrawn on medical grounds because in each case they had developed cardiovascular disease.

Thirteen of the patients have completed at least one year of therapy without recurrence.

Eighteen patients have to date developed recurrent ulceration, 15 of these within the first year. The mean time interval between healing of the previous ulcer and recurrence was 8·4 months. Thirteen of the 18 patients were receiving the placebo and five the active drug.

Although in this study the incidence of recurrent ulceration in those receiving deglycyrrhizinized liquorice was less than in the control group, the results did not reach statistical significance. However, it is concluded that the long-term treatment of patients with previous gastric ulceration using known ulcer-healing drugs may be a practical proposition in the majority of patients.

Is a gastroenterostomy a pre-malignant condition?

DAVID C. GOUGH AND JOHN L. CRAVEN (*Department of Surgery, Llandough Hospital, Penarth*) There have been numerous inconclusive reports in the literature linking previous gastric surgery with the subsequent development of carcinoma of stomach. We have analysed 15 patients in a series of 704 proven cases of carcinoma of stomach presenting on average 14 years later, and are of the opinion that a gastrojejunal anastomosis is a premalignant condition. The subsequent risk of malignant change is of the same order as in patients with proven pernicious anaemia.

Gastritis is commonly associated with gastric and duodenal ulceration, increasing age, previous gastric surgery and carcinoma but the histological appearance of intestinal metaplasia is regarded by many as a premalignant lesion[1]. This change can be shown in association with gastrojejunal anastomosis in almost 100% of cases but is much less common after pyloroplasty or Billroth I reconstruction[2]. It has been shown that malignant change can be induced experimentally in stomachs with gastrojejunal anastomosis much more readily in the intact organ[3].

We now feel that there is sufficient clinical, pathological and experimental evidence to support the view that a gastrojejunal anastomosis is a premalignant condition.

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Dietary and smoking habits in gastric cancer: A detailed study of 64 cases and controls

R. H. P. WILLIAMS, JULIA SMITH, T. J. COLE, AND J. L. CRAVEN (*Department of Surgery, Llandough Hospital, Penarth, Glamorgan*) The possibility of an association between carcinoma of the stomach and diet has been investigated several times with inconclusive results (Acheson and Doll, 1964). We have undertaken a detailed enquiry into the past and present dietary and smoking habits of 64 proven gastric cancer sufferers and an equal number of controls. Both groups were individually matched for sex, age, social class, civil state and place of domicile. Interviews were conducted in the subjects' homes by a trained dietitian.

In both past and present diets the consumption of rice, beer, cider and parsley showed a statistically significant preponderance for the cancer group ($P = < 0{\cdot}01$). In the past diet root vegetables alone showed a similar highly significant association with the patient group. Cigar smoking was entirely limited to the patient group whereas cigarette and pipe tobacco consumption were evenly distributed ($P = < 0{\cdot}0002$).

This detailed enquiry among a limited but carefully matched group of patients and controls has highlighted several factors which appear to be positively associated with gastric cancer. It has laid the basis for a more contracted investigation to be carried out among a larger sample of the gastric cancer sufferers available to us in South Wales.

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New evidence for intact di- and tripeptide absorption

P. D. FAIRCLOUGH, D. B. A. SILK, M. L. CLARK, AND A. M. DAWSON (*Department of Gastroenterology, St. Bartholomew's Hospital, London*) Recent work from this laboratory has demonstrated new evidence for the intact uptake of the dipeptide glycyl-alanine into the jejunal mucosal cells of man[1]. The present study confirms this phenomenon for another dipeptide, glycyl-glycine, and also demonstrates intact tripeptide entry into intestinal mucosal cells for the first time in man.

A perfusion technique has been used to measure jejunal peptide, amino acid, electrolyte and water absorption from isotonic, isonitrogenous solutions containing 144 mmol/l glucine, 72 mmol/l diglycine and 48 mmol/l triglycine. Evidence suggesting intact di- and tripeptide absorption comprises: (1) Not only was glycine absorbed faster from glycyl-glycine solutions than from the equivalent amount of glycine in the free form, but glycine absorption from triglycine was significantly greater than from diglycine. (2) Calculations of total solute and water absorption showed that the observed isosmotic absorption could only take place if the bulk of di- and tripeptide disappearing from the lumen was absorbed into the mucosal cells intact. This is in marked contrast to the behaviour of disaccharides, where the available evidence[2] suggests that one needs to assume complete hydrolysis prior to entry into the mucosal cells for isosmotic absorption to take place.

Since it is thought that little intact peptide enters the portal circulation, these observations may have important effects on the concepts of the site of osmotic equilibration occurring during transport across the jejunal mucosa, and may suggest that the site of equilibration may not be in the lateral intercellular space as has formerly been suggested, but may be within the cell itself.

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Effect of sugars and cations on the small intestine transepithelial pd in man

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Changes in pd produced by the sugars—glucose, galactose, fructose and sucrose—in the gut lumen together with the influence of Na, K and Li, have been investigated in eight patients having had ileostomy and one with jejunostomy, using a technique already described[1]. Of the monosaccharides, both glucose (actively absorbed and metabolized) and galactose (actively absorbed but not metabolized) caused a rise in pd in both jejunum and ileum when the sugar (40 mmol/l) was substituted for mannitol in the lumen. In the jejunum pd changed from $-2{\cdot}0$ mv to $-12{\cdot}0$ mv and in the ileum from $8{\cdot}3 \pm 1{\cdot}0$ mv (SEM) to $-24{\cdot}8 \pm 2{\cdot}1$ mv, the sign indicating the polarity in the lumen. Fructose, not actively transported or metabolized, had no effect on pd.

Sugar-dependent pd was reduced by lowering Na concentration and abolished when choline or K was substituted for Na. Li, however, was a partially effective substitute for Na, with pd rising from $-8{\cdot}3 \pm 1{\cdot}0$ mv to $16{\cdot}7 \pm 0{\cdot}6$ mv in the ileum. The disaccharide, sucrose, was also found to promote increase of pd similar to that of glucose, with pd rising in both jejunum from $-2{\cdot}0$ to $-10{\cdot}0$ mv and in ileum from $-8{\cdot}3 \pm 1{\cdot}0$ mv to $18{\cdot}5 \pm 0{\cdot}6$ mv. Hypertonicity of the luminal solution reduced sugar-dependent pd in ileum by 30% and in jejunum it was completed abolished.

In conclusion, the increase of human small intestinal pd produced by actively transported monosaccharides and disaccharides appears to be markedly sodium-dependent and in the jejunum is greatly influenced by the reduction of fluid absorption but in the ileum it is only partially affected.

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Further investigations with pH microelectrodes into the jejunal microclimate in rat and man

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An acid layer, postulated to exist[1] at the surface of rat proximal jejunum and incorporated into a model for folic acid transport[2], was demonstrated using modified pH microelectrodes of tip depth approximately 30 microns. The electrodes had a 57 mV/pH unit response which was uniform and linear over the 4-9 pH range, a resistance of $0{\cdot}4 \times 10^{10}$ Ohms and gave 95% of their maximal response within 30 seconds. Cannulated everted sacs[3] had a transmural pd of $5{\cdot}9 \pm 0{\cdot}6$ (5) mV, mucosal glucose transfer of 102 ± 20 (8) μg/mg dry wt/hr and serosal water transfer of $0{\cdot}98 \pm 0{\cdot}42$ (8) mg/mg dry wt/hr in Krebs-Henseleit buffer containing 10 mM glucose, indicating that viable sacs were prepared.

Standardized measurements of one-minute duration gave a surface pH value of 5·70 for the duodenum, 5·83 for the proximal jejunum, 6·02 for the distal jejunum, 6·14 for proximal ileum and 6·54 for distal ileum in the same buffer: all results were significantly different ($P < 0{\cdot}001$) from the buffer pH of 7·29. In the absence of glucose in the buffer, surface pH values in all regions except distal ileum were higher ($P < 0{\cdot}005$) and after 60 minutes' incubation at 37°C moved toward luminal, ie, more alkaline pH values. Absence of bicarbonate, ie, incubation in phosphate buffer, did not affect the surface pH. Preliminary studies using human bopsy material indicate an apparent microclimate of pH 5·9. Two distinct models can be proposed which give a proximal jejunum limiting microclimate pH value of either 4·5 or between 3 and 4. This demonstrated pH microclimate will have consequences for all weakly ionizing substances having pK values in the microclimate pH region and may be a cause underlying malabsorption states.

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A comparative study of intestinal absorption in normal Indian and English subjects using a perfusion technique

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It is well recognized that there is a difference between the structural appearances of the small intestinal mucosa of normal Indian and English subjects[1]. The functional counterpart of this structural change is less well documented and is based principally on studies of fat and xylose excretion[2].

In this study a more direct method has been used to measure absorption of glycine, glycyl-glycine water and sodium in 10 normal Indians and six English subjects. When compared with the English group the Indian subjects showed marked impairment of absorption of all substances, the differences being highly significant. In the Indian subjects amino acid and dipeptide absorption was impaired to the same extent and thus the kinetic advantage of glycyl-glycine over free glycine was preserved.

In parallel with the impaired absorption glycyl-glycine peptidase activity was also strikingly reduced in all Indians. If the lowered absorptive capacity of the upper jejunum in the Indian subjects is representative of the whole small intestine, the findings may be of considerable nutritional significance, particularly in an area where for most people the dietary intake is inadequate.

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Breath tests in small bowel colonization

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Aspiration and culture of small intestinal fluid is an uncomfortable and difficult procedure. Therefore simple non-invasive tests are required. The C^{14} glycine-cholate breath test ($C^{14}GC$) has been used with some success but some colonizing bacteria do not deconjugate

bile salts, eg, enterobacteria. Ingested carbohydrates are metabolized by some bacteria, including enterobacteria, to produce hydrogen (H_2) which can be detected in the breath.

We have therefore investigated 17 patients with gastrointestinal symptoms in whom colonization was suspected. Each patient had jejunal aspiration and culture, a routine $C^{14}GC$[1] and a 50-g oral glucose load with interval breath H_2 sampling to two hours[2].

Twelve patients were colonized (> 10^3 organisms/ml of species found in blind loops); eight were $C^{14}GC$ positive, five of whom produced H_2 (> 20 ppm) whilst three did not. Thus four colonized patients were $C^{14}GC$ negative; of these three produced H_2 (and grew non-bile-salt deconjugating pathogens) and the fourth was negative to both breath tests. Thus each test failed to diagnose four cases but the combination of breath tests diagnosed 11 out of 12.

Of the five non-colonized patients four were $C^{14}GC$ positive and H_2 negative. (Three of these are now suspected of having terminal ileal disease.) The fifth was negative to both tests.

These data suggest that, due to the different metabolic properties of bacteria, it may be necessary to use a combination of breath tests in the diagnosis of small intestinal colonization. In addition breath H_2 may help to differentiate colonization from terminal ileal disease.

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The incidence of coeliac disease and HL-A8 in dermatitis herpetiformis

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The reported incidence of coeliac disease (CD) in patients with dermatitis herpetiformis (DH) varies greatly (50% to virtually 100%). Possible reasons are that diagnosis of DH is insufficiently specific or that criteria for CD are insufficiently sensitive. In diagnosing DH, dermal IgA deposits are suggested as being more reliable than clinical and histological features, and, in diagnosing CD, intraepithelial lymphocyte (IEL) counting is suggested as more sensitive than villous atrophy. A further aspect of the association between CD and DH is an increased incidence of HL-A8 in each.

This study was designed to assess the incidence of CD and HL-A8 in patients with DH using the above criteria and using multiple jejunal biopsies in most patients to detect patchy abnormalities.

Of 47 patients with DH, 36 had villous atrophy, one had increased IEL only and 10 had normal biopsies. The incidence of HL-A8 was 78% overall: 70% in those with abnormal biopsies and 90% in those with normal biopsies.

We conclude that 21% of DH patients have no evidence of CD and that there is an association of HL-A8 with DH independent of its association with coeliac disease.