

# The British Society of Gastroenterology

The 38th annual main meeting of the British Society of Gastroenterology (under the Presidency of Dr. Geoffrey Watkinson) and the 6th annual main meeting of the British Society for Digestive Endoscopy (under the Presidency of Dr. W. Sircus) were held at York University from 22 to 24 September last, preceded by a Teaching Day organised by The British Society of Gastroenterology. The social programme included receptions at the Guild Hall and Castle Museum together with both societies' annual dinners. The Plenary Scientific Session included the Sir Arthur Hurst Lecture given by John S. Fordtran entitled 'Food and acid secretion'. The size of the programme necessitated four simultaneous sessions for the remainder of the meeting. Abstracts of all papers given at the meeting are reproduced below.

## ENDOSCOPY

### Neuroleptanalgesia versus diazepam as a premedication for upper GI tract endoscopy

C. BIRT, GILLIAN DAVIES, AND B. STERRY ASHBY (*General Hospital, Southend*) Neuroleptanalgesia using phenoperidine and droperidol has been the standard medication for endoscopy at Southend for some years. In a clinical trial to assess this method 150 patients were allocated by random numbers to receive phenoperidine and droperidol or phenoperidine and diazepam or diazepam alone.

In the endoscopist's assessment cases with anatomical difficulties were excluded leaving 41, 45, and 40 patients respectively in the three groups. Both phenoperidine and droperidol and phenoperidine and diazepam received higher scores for patient tolerance than diazepam and showed a lower incidence of movement, retching, salivation, hiccough, gagging, and coughing during endoscopy.

At the follow-up 15 patients failed to return, leaving 46, 48, and 41 patients in the respective groups. Forty per cent of patients who had received diazepam complained of thrombophlebitis and 20% had complete amnesia for the whole procedure. Approximately 50% of those receiving diazepam had fully recovered the same day compared with only 15% of those receiving droperidol and 90% and 80% respectively the following day. The diazepam group showed the least number of adverse effects and the highest number of patients who were prepared to return for a repeat procedure.

We conclude that neuroleptanalgesia is best for the endoscopist but diazepam is preferred by the patient.

### Bacterial contamination of fiberoptic endoscopes

M. NOY (introduced), LYNNE HARRISON (introduced), G. K. T. HOLMES, R. H. SAGE (introduced), AND R. COCKEL (*Selly Oak Hospital, Birmingham*) The clinical relevance of bacterial contamination of upper gastrointestinal endoscopes is controversial despite reports of bacteraemia after many types of endoscopy<sup>1</sup> and fatal *Pseudomonas* septicaemia after fibre-optic oesophagoscopy in leukaemia. The latter group was rendered liable to infection by granulocytopenia. We have encountered three previously healthy patients who, after endoscopy, developed severe infections with *Pseudomonas* of type identical with that on the endoscope. All were examined as emergencies before surgery for acute haemorrhage.

A quantitative survey of bacterial contamination of endoscopes and accessories showed that the insertion tubes were easily cleaned but simple washing was inadequate to disinfect channels within instruments. Irrigation of channels with Savlon left 12% heavily contaminated, rising to 50% by the next endoscopy session. Thorough irrigation with activated glutaraldehyde ( $\pm$  detergent) virtually eliminated vegetative organisms; prolonged immersion appeared unnecessary<sup>2</sup>.

The most important time for disinfecting instruments is immediately before use. This was shown by a study of oral flora before and after endoscopy. Of 124 patients from 25 sessions, 19 became colonised by bacteria from the endoscope (usually *Pseudomonas aeruginosa*); 18 were first on the list. Since routinely disinfecting instruments and accessories with glutaraldehyde before use, oral colonisation has been eradicated.

## References

- <sup>1</sup>Shull, J. H., Greene, B. M., Allen, S. D., Dunn, C. W., and Schenker, S. (1975). Bacteraemia with upper gastrointestinal endoscopy. *Annals of Internal Medicine*, 83, 212-214.
- <sup>2</sup>Axon, A. T. R., Phillips, J., Cotton, P. B., and Avery, S. A. (1974). Disinfection of gastrointestinal fibre endoscopes. *Lancet*, 1, 656-658.

### Varioliform gastritis or superficial hypertrophic gastritis

C. ANDRE, R. LAMBERT, B. MOULINIER, AND B. BUGNON (*Centre d'Endoscopie, Pavillon H, Hospital Edouard Herriot, Lyon, France*) Ninety cases of varioliform gastritis have been observed. This disease deserves its place in the field of inflammatory gastropathies on morphological, clinical, and physiopathological grounds.

1. Gastritis attacks the fundus. The topography of the nodules is ulcerated, hence the name varioliform gastritis or even erosive gastritis.

2. On the clinical level, the main symptoms and signs are epigastric pain, often of an atypical ulcerous nature, dyspeptic problems with nausea and gastric intolerance, and weight loss. Radiographs show large longitudinal folds in the fundus and characteristic rosette images in the antrum. Endoscopy shows the topography of the lesions: ulceration at the top of the swellings. The disease is characterised by acute episodes, the symptoms lasting several weeks, and relapses are quite frequent. Anatomical recovery always takes place later than clinical recovery.

3. The percentage of plasmocyte IgE from 12% in the fundus and 11% in the antrum when it remains normal in common inflammatory gastritis. Treatment by a stabiliser of mast cells (sodium cromoglycate) may be advised, because it often

coincides with a clinical improvement. In seven subjects the IgE plasmocytes were measured before and after the treatment: their percentage changed from 14 to 4.

#### Assessment of observer error in upper gastrointestinal endoscopy

R. J. HOLDEN AND G. P. CREAM (*Gastrointestinal Centre, Southern General Hospital, Glasgow*) There are few assessments of the error inherent in endoscopy. In this study two experienced observers have independently and sequentially examined the oesophagus, stomach, and duodenum of 31 patients attending a routine endoscopy clinic. Each observer assessed the presence or absence of 16 features in the oesophagus, 29 in the stomach, and 15 in the duodenum. To each feature assessment a probability value was attached using the probability scale 0-1.

Agreement was present in 97.4% of the 496 oesophageal assessments, 91.5% of the 883 gastric assessments, and 85.46% of the 405 duodenal assessments. Agreement about the normality or abnormality of the oesophagus, 93%; stomach, 87%; and duodenum, 89%; and agreement about the presence or absence of focal chronic lesions (ulcer, tumour) greater than 93%, was high. Disagreements about lesser signs were much greater—for example, gastric mucosal redness, 42% disagreements; gastritis 25% disagreement.

The probabilities attached to discordant assessments of chronic lesions were low (<0.9) indicating uncertainty by both observers. Disagreements over lesser signs were more strongly expressed—for example, 69% of disagreements over mucosal redness were given probabilities of >0.9 by each observer. An awareness of such error should influence the writing and interpretation of endoscopy reports.

#### Comparison of 'early gastric cancer' in Britain and Japan

D. M. D. EVANS, J. L. CRAVEN, F. MURPHY, AND B. CLEARY (*Llandough Hospital, Penarth, and York District Hospital*). Introducer: J. L. CRAVEN, *York District Hospital*) Before the introduction of endoscopy, four out of 720 cases of gastric cancer at Llandough Hospital were diagnosed before the cancer had breached the muscularis propria, an incidence of 0.5%. Using endoscopy and endoscopic biopsy, 10 out of 101 cases of gastric cancer were diagnosed at this 'early' stage, an incidence of 10.1%. Four additional 'early

gastric cancers' were found in neighbouring hospitals and at York District Hospital. Their clinical, morphological, and histological characteristics were compared with those of Japanese 'early gastric cancers'<sup>1,2,3</sup> and revealed a remarkable similarity. The results of this study suggested that a higher proportion of British gastric cancer could be diagnosed at an 'early' stage by more intensive investigation of dyspeptic patients using up-to-date radiological techniques, fiberoptic endoscopy, and endoscopic biopsy.

#### References

- <sup>1</sup>Nakamura, K., Sugano, H., Takagi, K., and Fuchigami, A. (1967). Histopathological study on early carcinoma of the stomach. *Gann*, 58, 377-387.
- <sup>2</sup>Murakami, T. (1972). Pathomorphological diagnosis, in *Early Gastric Cancer*, pp. 53-58. *Gann Monograph II*. Edited by T. Murakami, University Park Press: Tokyo.
- <sup>3</sup>Mochizuki, T. (1972) Method for histopathological examination of early gastric cancer, in *Early Gastric Cancer, Gann Monograph II*, pp. 57-62. Edited by T. Murakami. University Park Press: Tokyo.

#### ERCP and surgery in recurrent acute pancreatitis

P. B. COTTON AND J. R. CROKER (*Gastrointestinal Unit, The Middlesex Hospital, London*) ERCP performed on 135 patients between recurrent attacks of acute pancreatitis showed normal pancreatography in 43% of 123 successful studies, major diffuse changes in 14%, and obstruction, pseudocyst, or stricture in 32%. Three patients had cancer and 11 important congenital duct anomalies. Retrograde cholangiography showed stones in 13 patients with previous negative radiology. The 63 patients studied in 1971-74 were reviewed at two to five years. Progress had been excellent in 32, good in 11, and bad in 11; three patients had died (two of unrelated conditions), and six could not be traced. Surgical procedures based on the ERCP findings had been performed in 31 patients: cholecystectomy (nine), sphincter procedures (seven), pseudocyst drainage (six), left hemipancreatectomy (seven), total pancreatectomy (two). Cholecystectomy alone gave excellent results even when pancreatography was abnormal. Subsequent drinking habit in patients with alcohol abuse (28/49 men; 2/14 women) was the major determinant of prognosis with or without surgery. Only one patient made good progress despite continuing to drink. Relapsing acute pancreatitis is a benign

condition. ERCP provides a good surgical map, but the outcome is mainly dependent on removal of the initiating cause.

#### Routine endoscopic biopsies: a new and accurate tool to investigate gut endocrinology

M. G. BRYANT, S. R. BLOOM, J. M. POLAK, S. HOBBS, W. DOMSCHKE, S. DOMSCHKE, P. MITZNEGG, H. RUPPIN, AND L. DEMLING (introduced by S. R. BLOOM) (*Departments of Medicine and Histochemistry, Royal Postgraduate Medical School, London, and Medizinische Universitätsklinik, Erlangen, W. Germany*) The tissue concentrations of intestinal hormones in alimentary disease has hitherto been studied only in surgical specimens, and the information is therefore of little diagnostic value. This study was therefore undertaken, firstly, to determine whether the gut hormones can be reliably measured in extracts of small mucosal biopsies and, secondly, to establish from this normal reference values and distribution pattern.

Parallel biopsies were taken from the antrum, duodenum, and jejunum of nine patients for analysis of protein and DNA content and quantitative immunocytochemistry. A specially adapted micro-radioimmunoassay was used to measure hormonal content. Gastrin was maximal in the antrum ( $280 \pm 68$  pmol/g;  $251 \pm 78$  cells/mm<sup>2</sup>). VIP was widely distributed but was highest in the duodenal bulb ( $96 \pm 25$  pmol/g;  $52 \pm 11$  cells/mm<sup>2</sup>). Secretin, GIP, and motilin were maximal in the descending duodenum ( $128 \pm 52$ ,  $70 \pm 8$ ,  $63 \pm 10$  pmol/g;  $16 \pm 4$ ,  $30 \pm 8$ ,  $60 \pm 10$  cells/mm<sup>2</sup> respectively), while enteroglucagon was detectable only beyond the ligament of Treitz ( $13 \pm 4$  pmol/g;  $10 \pm 1$  cells/mm<sup>2</sup>).

This methodology at last allows study of the physiology of the non-circulating hormones found in the gut paracrine system. Investigation of the level of mucosal endocrine hormones and their cell pathology in routine endoscopy clinic biopsies should provide an important new tool for the preoperative diagnosis of alimentary disease.

#### Endoscopic Celestin intubations for inoperable malignant dysphagia: a new use for the Foley catheter

E. W. GILLISON, J. KHAN, AND J. M. ELLIOTT (*Department of Gastroenterology, Kidderminster General Hospital*) In complete agreement with Ferguson and Atkinson<sup>1</sup> concerning the high mortality of laparo-

tomy and pull-through for malignant dysphagia, an attempt was made to emulate their results using the endoscopic method they described to dilate and insert Celestin tubes.

Earlier experience of perforation of the oesophagus without radiographic control prompted a study using the image intensifier in the X-ray department for 13 consecutive dilatations in nine patients with malignant dysphagia. Seven dilatations and intubations were performed for advanced carcinoma of the oesophagus, three for carcinoma of the gastric cardia, and three for constriction of the oesophagus by advanced bronchial carcinoma. One of the bronchial carcinomas had produced a fistula into the oesophagus which was sealed by the Celestin tube.

Only one patient died in hospital secondary to myocardial insufficiency and the remainder went home after two days.

By employing a gauge 28 Foley catheter over the flexible Eder-Puestow system, each Celestin tube could be inserted into the malignant stricture and beyond. Dislocation of the tube had occurred in four of the patients and all were successfully extracted by inflating the balloon of the catheter against the inner wall of each Celestin tube. Replacement tubes were inserted using the same technique.

#### Reference

- <sup>1</sup>Ferguson, R., and Atkinson, M. (1976). Endoscopic insertion of the Celestin tube in patients with inoperable carcinoma of the cardia. *Gut*, 17, 832.

#### ABSORPTION/MALABSORPTION AND COELIAC DISEASE

#### Coeliac disease: diagnostic hormone profile

H. S. BESTERMAN, J. STEWART, S. GUERIN, R. MODIGLIANI, C. N. MALLINSON, AND S. R. BLOOM (Royal Postgraduate Medical School, Hammersmith Hospital, London, West Middlesex Hospital, Isleworth, Hoptal Saint-Lazare, Paris, France, and Greenwich District Hospital, London) Coeliac disease is underdiagnosed and this may be due to the absence of a simple screening test. We have previously demonstrated a marked impairment of secretin release<sup>1</sup>, as this hormone is localised to the area of maximal mucosal pathology. In view of the increased cell turnover in coeliac disease, we have now investigated the release of the trophic hormone, enteroglucagon.

Eleven patients with biopsy-proven active coeliac disease, 13 patients with coeliac disease on gluten-free diet with good clinical and histological response, and 13 age- and sex-matched normal subjects were studied with a standardised breakfast.

Plasma levels of gastrin, motilin, pancreatic polypeptide, VIP, and enteroglucagon were measured. Plasma enteroglucagon in controls rose from  $28 \pm 7$  pmol/l to  $45 \pm 11$  pmol/l at 180 minutes. Patients with active coeliac disease had raised basal levels ( $94 \pm 31$  pmol/l), which rose dramatically to  $263 \pm 62$  pmol/l at 180 minutes ( $P < 0.005$ ). Patients with treated coeliac disease had normal enteroglucagon levels. There were no significant differences in the levels of the other hormones.

Thus, measurement of the gut hormone profile demonstrates the specific defect in the diseased small intestine and a considerable compensatory increase of the ileal hormone, enteroglucagon. This pattern of change appears to be highly specific to coeliac disease and may serve as a convenient new diagnostic test.

#### Reference

- <sup>1</sup>Bloom, S. R., Patel, H. R., and Johnston, D. I. (1976). Failure of secretin release in coeliac disease. *Gut*, 17, 812.

#### Cholecystokinin abnormalities in coeliac disease

J. M. POLAK, M. V. MCCROSSAN, C. M. TIMSON, D. R. JOHNSTON, D. HUDSON, M. SZELKE, A. G. E. PEARSE, AND S. R. BLOOM (Departments of Histochemistry and the Endocrine Unit Royal Postgraduate Medical School, London, and Department of Paediatrics, Nottingham Medical School) In coeliac disease there is a diminished secretion of both bicarbonate and enzymes by the pancreas. This is seen in response to a normal meal, to intraluminal acidification (known to release secretin), or to intraluminal aminoacid perfusion (a stimulant of CCK release)<sup>1</sup>. However, the pancreatic secretion is normal after intravenous injections of CCK and secretin, thus indicating that the pancreas itself can function normally but lacks the appropriate hormonal signal (CCK-secretin) from the gut. We have previously shown that the S cells in coeliac disease are hyperplastic and have increased hormone storage<sup>2</sup>. This fits with the functional failure of secretin release after intraduodenal infusion of acid<sup>3</sup>.

Highly specific antibodies to CCK have recently become available and we were therefore able to investigate the state of the CCK producing cells in coeliac disease.

Jejunal biopsies were taken from seven children with coeliac disease and five controls with suspected malabsorption but normal mucosa. Quantitative immunocytochemistry using an automatic television image analyser computer showed that the number of CCK cells in the coeliac biopsies increased by 37% (mean  $7.9/\text{mm}^2 \pm 1.98$ ) (normal mean  $5.7 \pm 0.82$ ). The CCK cells were also larger than normal and strongly immunofluorescent, indicating high storage of hormone. This indicates that CCK release, like secretin, is impaired in patients with coeliac disease.

#### References

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<sup>2</sup>Polak, Julia, M., Pearse, A. G. E., Van Noorden, Susan, Bloom, S. R., and Rossiter, Mary, A. (1973). Secretin cells in coeliac disease. *Gut*, 14, 870.  
<sup>3</sup>Bloom, S. R., Patel, H. R., and Johnston, D. I. (1976). Failure of secretin release in coeliac disease. *Gut*, 17, 812.

#### Inhibition of leucocyte migration by gliadin in patients with gastrointestinal disease: its specificity with respect to gliadin and coeliacs

P. ASQUITH AND M. R. HAENEY (Frazier Squire Metabolic Research Unit, East Birmingham Hospital and, Department of Experimental Pathology, University of Birmingham) Specific leucocyte migration inhibition (LMI) is generally regarded as an *in vitro* test of cell-mediated immunity. LMI to gluten has been reported in patients with adult coeliac disease<sup>1,2</sup>. We have evaluated the test with particular regard to antigen and disease specificity.

LMI to  $\alpha$ -gliadin,  $\alpha$ -lactalbumin, BCG and PPD has been estimated in four groups of subjects: normal-diet coeliacs (15), gluten-free diet coeliacs (11), patients with other gastrointestinal diseases (20), and age- and sex-matched healthy controls (26). LMI to BCG and PPD was similar in all four subject groups, confirming that the potential cellular responsiveness of coeliac patients is normal.

Leucocyte migration in the presence of  $\alpha$ -gliadin was significantly inhibited in treated coeliacs compared with untreated coeliacs, healthy controls, and patients with other intestinal diseases, but no significant inhibition was seen in untreated

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coeliacs compared with the control groups. In contrast, no significant differences were found in the response to  $\alpha$ -lactalbumin in any of the four groups.

Significant inhibition to  $\alpha$ -gliadin was observed in 9/11 coeliacs on a gluten-free diet, 5/15 untreated coeliacs, 1/26 healthy controls, and 1/20 gastrointestinal patients. Inhibition to  $\alpha$ -lactalbumin occurred in 2/11 treated and 3/15 untreated coeliacs, 3/26 normal subjects and 3/20 patient controls.

LMI to  $\alpha$ -gliadin appears specific for adult coeliac disease and occurs more frequently in treated than in untreated coeliac patients.

#### References

- <sup>1</sup>Bullen, A. W., and Losowsky, M. S. (1976). Cell-mediated immunity (CMI) to gluten fraction III (GF III) in adult coeliac disease (ACD). *Gut*, 17, 813.
- <sup>2</sup>Douwes, F. R. (1976). Gluten and lymphocyte sensitisation in coeliac disease. *Lancet*, 2, 1353.

#### Increased prevalence of epilepsy in coeliac disease

J. M. LAIDLAW, R. G. CHAPMAN, D. G. COLIN-JONES, O. EADE, AND C. L. SMITH (*Gastrointestinal Clinics, The Royal and Queen Alexandra Hospitals, Portsmouth, and the Professorial Medical Unit, Southampton*) A number of neurological disorders may occur in association with coeliac disease<sup>1</sup>, but an increased prevalence of epilepsy in this condition has not previously been documented. In view of a strong clinical impression that the prevalence is increased, the following survey was carried out.

One-hundred-and-eighty-five treated presumed coeliac patients who were members of the Coeliac Society in Hampshire were sent a questionnaire inquiring about the occurrence and frequency of fits, black-outs, and other medical conditions: 165 patients returned the questionnaire. Nine patients were considered to be epileptics, giving a prevalence of 5.45%. A further six patients were considered to be possible epileptics. In seven out of nine cases the epilepsy was temporal lobe in type.

The national prevalence of epilepsy of all types is approximately 0.5%. In order to confirm this figure, 165 age- and sex-matched controls were circulated with a similar questionnaire. Of 92% who replied there was one possible case of epilepsy, giving a prevalence of 0.6%.

These results show that there is a higher prevalence of epilepsy in coeliac disease ( $\chi^2 = 4.47$ ,  $P < 0.05$ ).

The reasons for this are unknown but have clear implications in patient care.

#### Reference

- <sup>1</sup>Morris, J. S., Aidukiewicz, A. B., and Read, A. E. (1970). Neurological disorders and adult coeliac disease. *Gut*, 11, 549-554.

#### Distribution of neurotensin in man: a peptide hormone affecting carbohydrate metabolism

A. M. J. BUCHAN, J. M. POLAK, S. SULLIVAN, S. R. BLOOM, AND A. G. E. PEARSEN (*Departments of Histochemistry and Medicine, Royal Postgraduate Medical School, London*) Neurotensin (NT) is a tridecapeptide originally isolated from bovine hypothalamus. Recent studies have suggested that neurotensin-like immunoreactivity may be present in the rat gut in quantities larger than those found in the nervous system. Neurotensin has a wide spectrum of actions including production of hypotension, gut contraction, increased vascular permeability, haemoconcentration, hyperglycaemia, and hyperglucagonaemia.

We report the results of studies into the distribution and localisation of NT in human intestine. The study involved radioimmunoassay and immunocytochemistry of fresh surgical and endoscopic samples. The intestinal distribution shows the highest concentration in ileal mucosa (16.2 pmol/g: 31 cells/mm<sup>2</sup>) a significant amount in jejunum (2.82 pmol/g: 1-10 cells/mm<sup>2</sup>) with traces present in other areas. We have established the exact cellular origin of NT in the gut by the semithin technique. The morphology of the cell is characteristic of a typical endocrine cell with a connection to the lumen *via* microvilli and the storage granules grouped at the basement membrane. The identifying feature is the electron dense, uniformly round large (300 nm) secretory granules. The cell has been named the N cell as it was previously undescribed. The circumscribed localisation to the lower small intestine suggests that NT may be important in the post-digestive process.

#### Mucosal adherence of human enteropathogenic *E. coli* (EPEC) is mediated by a transmissible plasmid

A. S. MCNEISH, P. H. WILLIAMS, N. EVANS, P. TURNER, AND R. H. GEORGE (*University of Leicester and Birmingham Children's Hospital*) In pigs, virulent strains of EPEC possess the plasmid-coded surface antigen K88 that promotes adherence of

the organism to pig intestine, and that is an important virulence determinant. We have previously shown that a human EPEC (serotype 026K60H11) can adhere specifically to the mucosa of human foetal small intestine<sup>1</sup>. Now we have evidence that this adherence is mediated by a transmissible plasmid.

Strain 026K60H11 was grown in liquid culture to label its DNA uniformly with 3H-thymidine. Sarkosyl-lysed cells were subjected to ethidium bromide-caesium chloride buoyant density centrifugation. Almost 30% of the DNA banded at the density characteristic of plasmid DNA. Analysis of this material in neutral sucrose density gradients showed that it comprised a larger plasmid species with a molecular weight of 50-60 megadaltons, and two smaller species.

We transferred the adherence characteristic by bacterial conjugation from the EPEC strain to 15% of a recipient strain of *E. coli* K12. Analysis of the DNA of adherent clones of K12 showed that 9% was in the plasmid form, identical with the plasmid of 50-60 megadaltons in the donor EPEC.

We conclude that this plasmid (that we have designated pLG101) mediates mucosal adherence in some strains of human EPEC, and is likely to be an important determinant of virulence.

#### Reference

- <sup>1</sup>McNeish, A. S., Turner, P. J., Fleming, J., and Evans, N. (1975). Mucosal adherence of human enteropathogenic *Escherichia coli*. *Lancet*, 2, 946-948.

#### Studies in primary hypomagnesaemia: evidence for a defect in carrier-mediated transport of magnesium

P. J. MILLA, O. H. WOLFF, AND J. T. HARRIES (*The Hospital for Sick Children, Great Ormond Street, and Institute of Child Health, London*) In comparison with other divalent cations, the intestinal absorption of magnesium (Mg<sup>++</sup>) has not been widely studied. Primary hypomagnesaemia is a rare disorder which is inherited in an autosomal recessive fashion, and which is associated with defective absorption of Mg<sup>++</sup>. The precise site and nature of the transport defect has not been defined.

We have investigated such a patient by means of metabolic balances as well as by a steady-state perfusion technique. Metabolic balance studies showed net malabsorption of Mg<sup>++</sup> during infancy. At the age of 3 years perfusion of the proxi-



mal jejunum with  $Mg^{++}$  (1 and 2 mM) showed secretion of  $Mg^{++}$ , compared with mean control values of 0.019 and 0.025  $\mu\text{mol}/\text{min}/\text{cm}$  respectively; at 10 mM absorption occurred at a rate of 0.13 compared with a mean control value of 0.15. The kinetics of  $Mg^{++}$  transport were studied in a small group of control children, and the results suggest a saturable mechanism at low concentrations ( $K_m$  3.7 mM;  $V_{max}$  0.078  $\mu\text{mol}/\text{min}/\text{cm}$ ), with a superimposed diffusional component at high concentrations.

These results suggest that  $Mg^{++}$  is transported by a carrier-mediated mechanism at low concentrations, and that this is defective in primary hypomagnesaemia.

#### Urea, uric acid, and creatinine fluxes through the small intestine of man

V. S. CHADWICK, J. D. JONES, J.-C. DEBONGNIE, T. GAGINELLA, AND S. F. PHILLIPS (*Gastroenterology Unit, Mayo Clinic, St Mary's Hospital, Rochester, Minnesota 55901, USA*) Radioisotopic tracer studies have shown that approximately 7 g urea<sup>1</sup>, 200 mg uric acid<sup>2</sup>, and up to 700 mg creatinine<sup>3</sup> can be degraded by intestinal bacteria each day. How these metabolites reach the colon is controversial, but as the colon is not very permeable to these molecules it is thought that they cross into the small bowel lumen and enter the colon in ileal fluid. We measured daily fluxes of urea, uric acid, and creatinine through distal duodenum and terminal ileum in four normal subjects using slow perfusion techniques to determine input to, and output from, the small intestine.  $906 \pm \text{SEM } 105$  mg urea,  $112 \pm 43$  mg uric acid and  $94 \pm 17$  mg creatinine entered the small intestine from the duodenum and  $759 \pm 75$  mg urea,  $89 \pm 26$  mg uric acid, and  $93 \pm 16$  mg creatinine were delivered to the colon daily.

Concentrations of urea and uric acid in ileal fluid remained constant over the 24 hours, so that colonic inputs were directly related to the rate of ileal flow. However, creatinine concentrations increased after meals, suggesting conversion of dietary creatine to creatinine within the lumen.

We conclude that, as the measured colonic input of urea, uric acid, and creatinine from the ileum accounts for only a small proportion of their estimated daily intestinal breakdown, large amounts of these metabolites must be excreted directly into the colon from the blood.

#### References

- <sup>1</sup>Walser, M., and Bodenlos, L. J. (1959). Urea metabolism in man. *Journal of Clinical Investigation*, **38**, 1617.  
<sup>2</sup>Sorensen, L. B. (1959). Degradation of uric acid in man. *Metabolism: Clinical and Experimental*, **8**, 687.  
<sup>3</sup>Jones, J. D., and Burnett, P. C. (1974). Creatinine metabolism in humans with decreased renal function: Creatinine deficit. *Clinical Chemistry*, **20**, 1204, 1212.

#### Metabolism of dietary fibre components in man, as assessed by breath hydrogen and methane

K. TADESSE AND M. A. EASTWOOD (*Wolfson Laboratory, Gastrointestinal Unit, Western General Hospital, Edinburgh*) If man is able to digest dietary fibre, it is by virtue of his intestinal bacteria. Anaerobic bacterial metabolism of oligo- and polysaccharides results in products including hydrogen and methane. These gases diffuse to the blood and are excreted in the expired air, a sample of which can be measured by gas-chromatography<sup>1</sup>.

Normal individuals, eating regularly, excrete less than 20 ppm of hydrogen. There is a regular and typical pattern of change during the day, with peak production in the morning and early afternoon. Fasting minimises the morning and afternoon rise and the variation during the day. Methane excretion is not influenced by diet and is typical for the individual.

We have studied the metabolism of polysaccharides (cellulose, hemicellulose, pectin, starch), oligosaccharides (raffinose, lactulose), and lignin. Ten or 20 g of the substances in water were eaten raw in the morning and the end-expiratory breath hydrogen and methane<sup>2</sup> followed during the day while otherwise fasting.

Raffinose and lactulose increased total hydrogen production and peak values of 50-60 ppm were common. Hemicellulose increased total breath hydrogen to a lesser extent and peak values of 30 ppm were attained by some. The other polysaccharides and lignin studied had no effect. Physical properties—for example, particle size—did not influence hydrogen production. Methane excretion is not affected by any of the chemicals.

This suggests that, after acute administration, hemicellulose, lactulose, and raffinose are metabolised by a mechanism involving hydrogen and methane production, whereas the other polysaccharides and lignin are not.

#### References

- <sup>1</sup>Calloway, D. H., and Murphy, E. L. (1968). The use of expired air to measure intestinal gas formation. *Annals of the New York Academy of Science*, **150**, 82-95.  
<sup>2</sup>Metz, G., Gassull, M. A., Leeds, A. R., Blendis, L. M., and Jenkins, D. J. A. (1975). A simple method of measuring breath hydrogen in carbohydrate malabsorption by end-expiratory sampling. *Clinical Science and Molecular Medicine*, **50**, 237-240.

#### Effect of maltose on the absorption of glucose in the jejunum in man

G. I. SANDLE, R. W. LOBLEY, AND R. HOLMES (*University Department of Gastroenterology, Manchester Royal Infirmary*) *In vitro* work suggests disaccharidase-linked glucose transport from maltose in addition to the monosaccharide transport system<sup>1</sup>.

To investigate this, 20 cm segments of proximal jejunum were perfused by double-lumen tube in six normal subjects using isotonic glucose-saline solutions (flow rate 21 ml/min) containing PEG 5 g/l. Active glucose transport was saturated with 166.5 mM glucose and the rates of absorption (mM/20 cm/10 min  $\pm$  SE) from 222 mM glucose ( $8.84 \pm 0.8$ ) and 277.5 mM glucose ( $10.21 \pm 0.68$ ) were not significantly different.

Four normal subjects were perfused with isotonic solutions in sequence containing 35 mM maltose, 222 mM glucose, 35 mM maltose + 222 mM glucose, and finally 111 mM maltose. Absorption rates from 222 mM glucose in the two groups ( $8.84 \pm 0.8$  and  $10.16 \pm 0.29$ ) were not significantly different. Absorption from the maltose + glucose mixture ( $11.58 \pm 0.3$ ,  $0.02 < 2P < 0.025$ ) and from 111 mM maltose ( $11.33 \pm 0.46$ ,  $0.025 < 2P < 0.05$ ) both exceeded that from glucose ( $10.16 \pm 0.29$ ). Absorption rates from maltose + glucose and 111 mM maltose were not significantly different. Maltose hydrolysis ( $19.3 \pm 1.41$ ) was inhibited by glucose ( $10.76 \pm 1.83$ ,  $0.025 < P < 0.05$ ).

It is concluded that (1) disaccharidase-linked glucose transport was not confirmed *in vivo* in man, (2) increased glucose absorption from maltose + glucose may be due to diffusion, (3) glucose is absorbed more rapidly from 111 mM maltose than 222 mM glucose, (4) maltose hydrolysis is inhibited by high glucose concentrations.

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### Factors influencing intestinal mucosal hypoplasia during total parenteral nutrition (TPN) in rats

C. A. HUGHES, A. PRINCE, AND R. HERMON DOWLING (*Guy's Hospital and Medical School, London*) During TPN, rat intestinal mucosa becomes hypoplastic<sup>1,2,3</sup> but it is not known how quickly this occurs nor whether it is due to (1) exclusion of luminal nutrients, (2) secondary pancreatic hypofunction, (3) reductions in trophic hormones, or (4) changes in bacterial flora. We therefore established speed of change in jejunal and ileal structure and function, pancreatic mass and aerobic + anaerobic mucosal bacterial counts after three to 15 days of TPN before studying the effect on intestine and pancreas of 40  $\mu\text{g}$  CCK octapeptide or 1.75 units secretin  $\text{kg Bw}^{-1} \text{day}^{-1}$  during 10 days TPN.

Jejunal villus height fell from  $423 \pm \text{SEM } 5.1 \mu\text{m}$  before to  $342 \pm 28$ ,  $313 \pm 19$ ,  $301 \pm 13$ ,  $295 \pm 13$  at three, six, 10, and 15 days. Apparent  $V_{\text{max}}$  (*in vivo* galactose absorption; 4-64 mM fell from  $44 \pm 4$  to  $19.4 \pm 2 \text{ mmol/cm intestine}^{-1} \text{h}^{-1}$  but 'carrier affinity' increased so that  $K_m$  fell from  $36.7 \pm 5$  to  $13.2 \pm 1.5 \text{ mmol/l}$ . Pancreatic weight, DNA, and protein also decreased within three days ( $P < 0.001$ ).

In the doses used, neither CCK nor secretin prevented intestinal hypoplasia but CCK prevented pancreatic hypoplasia ( $374 \pm 8.6 \text{ mg/100 g BW}$  without and  $568 \pm 42.7$  with CCK).

Viable bacterial counts ( $\log_{10}/\text{g}$  mucosal wet weight) also decreased, jejunal anaerobes falling from  $6.58 \pm 33$  before to  $4.32 \pm 0.4$  after 10 days TPN ( $P < 0.001$ ).

In summary, intestinal mucosal hypoplasia and hypofunction, associated with reductions in microbial flora, develop within three days of TPN and are prevented neither by CCK nor secretin. CCK prevented the pancreatic hypoplasia of TPN.

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### Effect of folate deficiency on mucosal DNA synthesis during recovery from tropical malabsorption (TM)

A. M. TOMKINS, M. MCNURLAN, AND S. WRIGHT (*Clinical Nutrition and Metabolism Unit, Hospital for Tropical Diseases, Department of Human Nutrition, London School of Hygiene and Tropical Medicine*) The importance of mucosal folate deficiency in impairment of epithelial regeneration during recovery from TM is unclear. An *in vitro* system for jejunal biopsy specimens<sup>1</sup> to assess the essential folate-mediated step of thymidylate synthesis (methylation of deoxyuridine  $\rightarrow$  thymidylate) in DNA synthesis of mucosal cells has been used to monitor effects of therapy of TM.

Control subjects incorporated  $234 \pm 76 \text{ dpm H}^3\text{Thymidine}/\mu\text{g DNA}$  and TdR/DNA was suppressed to below 20% by the addition of  $2 \times 10^{-4}$  deoxyuridine (dU) via an effect on the folate dependent *de novo* pathway. TdR/DNA in seven patients was higher than controls ( $607 \pm 86 P < 0.01$ ); dU failed to suppress TdR/DNA in six cases, indicating functional mucosal folate deficiency.

After four weeks tetracycline TdR/DNA fell in five cases with mucosal improvement ( $261 \pm 74 P < 0.05$ ). dU suppressed TdR/DNA in each and folic acid (100  $\mu\text{g/ml}$ ) addition produced no effect. In two cases, mucosal lesions deteriorated and dU failed to suppress TdR/DNA. Such changes imply that mucosal folate deficiency usually recovers rapidly after antibiotics but may continue and contribute to persisting mucosal lesions.

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### Absorption of antigen after oral immunisation and the induction of systemic tolerance

E. T. SWARBRICK AND C. R. STOKES (introduced by A. M. DAWSON) (*St. Mark's Hospital, London, and The Institute of Child Health, London*) *In vitro* experiments have suggested that prior feeding of intact protein antigens reduces their subsequent absorption<sup>1</sup>. These *in vitro* models have the disadvantage of altered per-

meability and we have therefore attempted to show the same phenomenon *in vivo*. Groups of mice were fed ovalbumin or saline for 14 days, rested for 14 days, and then challenged with intragastric ovalbumin. The concentration of ovalbumin in the circulation was measured 45 minutes later using a sensitive radioimmunoassay and was lower in those animals previously fed ovalbumin. As the clearance of  $^{125}\text{I}$ -ovalbumin from the circulation was not increased in these animals, it is concluded that antigen feeding induces immune exclusion by the gut.

Further groups of mice were fed antigen in the same dosage for the same length of time, but subsequently challenged with parenteral ovalbumin in complete Freund's adjuvant. Mice fed ovalbumin showed a reduced antibody response compared with controls. The phenomena of immune exclusion and orally induced systemic tolerance are therefore stimulated simultaneously and together would offer an effective way of dealing with relatively harmless ingested antigens.

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### Small intestinal changes induced by an elemental diet (Vivonex) in rats

L. M. NELSON, H. A. CARMICHAEL, R. I. RUSSELL, AND F. D. LEE (*Gastroenterology Unit and Department of Pathology, Royal Infirmary, Glasgow*) The importance of oral rather than intravenous nutrition in maintaining normal gut mass and function has been demonstrated in rats<sup>1</sup> and dogs<sup>2</sup> but the effect of different types of oral nutrition, especially elemental diets, on small bowel structure and function has not been fully investigated. We have investigated the effect of an elemental diet (Vivonex) on the morphology and enzyme activity of normal rat jejunum.

Three groups of rats were studied, with similar numbers in each group fed Vivonex and normal diet. Groups 1 and 3 ( $n = 12$  in both cases) were three months and group 2 ( $n = 9$ ) a one month study.

The ratio of crypt height: villus height was significantly reduced in the Vivonex fed rats compared with controls in all three groups ( $P < 0.01$ ,  $P < 0.05$ ,  $P < 0.01$ ). No control rat had a ratio  $< 0.22$  and only one Vivonex fed rat had a ratio  $> 0.20$ .

Jejunal protein content, alkaline phos-

phatase, and disaccharidase activities were measured for rats in groups 2 and 3. Jejunal alkaline phosphatase activity was significantly increased in the Vivonex fed rats. Specific activity increased from  $3.52 \pm 0.43$  to  $5.37 \pm 0.42$   $\mu\text{mol}/30$  min/mg protein (mean  $\pm$  SEM) in group 2 and from  $3.24 \pm 0.21$  to  $3.88 \pm 0.25$   $\mu\text{mol}/30$  min/mg protein in group 3 ( $P < 0.05$  in both cases). Total activity per 10 cm segment was also increased ( $P < 0.02$ ,  $P < 0.05$ ).

These results suggest that the elemental diet Vivonex may increase the mature enterocyte population and improve enterocyte survival in normal rats. This emphasises the importance of oral nutrition, even to the normal small intestinal mucosa.

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#### Dietary fibre and drug absorption: the effect of pectin and bran on paracetamol absorption in the rat

R. C. BROWN, J. KELLEHER, B. E. WALKER, AND M. S. LOSOWSKY (*Department of Medicine, University of Leeds, St. James's Hospital, Leeds*) Fibre has profound effects on gastrointestinal function and is known to affect the absorption of nutrients. It is often given to patients taking drugs but there is surprisingly little information on whether fibre alters the effects of these drugs.

In rats fed a basal diet, with 18% pectin added, the urinary excretion of paracetamol in the first eight hours after an oral dose is greater than in rats fed basal diet alone (mean  $45.2 \pm \text{SEM } 4.9\%$  of dose v.  $20.4 \pm 4.3\%$ ,  $n = 6$ ,  $P = < 0.0025$ ). The cumulative excretion after 72 hours is the same.

In similar experiments an 18% bran diet had no effect.

Plasma free paracetamol levels are raised in pectin-fed rats at 30, 60, 90, and 120 minutes after oral paracetamol dosage ( $P = < 0.05$  at each time) suggesting that differences in absorption underlie the more rapid urinary excretion. Furthermore, absorption of paracetamol solution (10 mg/ml) perfused through the small bowel is greater in pectin-fed rats ( $49.4 \pm$

$3.5\%$  v.  $39.2 \pm 4.1\%$ ,  $n = 6$ ,  $P = < 0.005$ ). Differences in hepatic metabolism may play a part, as the plasma half-life of intravenously injected paracetamol is shorter in the pectin-fed rats ( $30.0 \pm 1.5$  minutes v.  $34.0 \pm 1.2$  minutes,  $n = 6$ ,  $P = < 0.05$ ), though the antipyrine half-lives are the same.

Our results show that fibre affects drug absorption and that the effect varies with the type of fibre. Unexpectedly pectin enhances rather than retards drug absorption. Pectin may also affect drug metabolism.

#### Osteomalacia in patients with small intestinal resection

JULIET E. COMPSTON, L. W. L. HORTON, AND B. CREAMER (*Gastrointestinal Research Unit, Rayne Institute, and Department of Surgical Pathology, St. Thomas' Hospital, London*) The prevalence of histological osteomalacia after small intestinal resection has been investigated in 25 patients, aged 22-72 years, by quantitative assessment of transilial biopsies<sup>1</sup>.

Eight patients (32%) had histological osteomalacia, severe in five and mild in three; only one was symptomatic. Definite radiological changes occurred in four of the eight, but two with severe osteomalacia showed no radiological abnormality. Serum calcium, phosphate, and alkaline phosphatase concentrations were normal in all three patients with mild osteomalacia, but alkaline phosphatase was raised in the five with severe osteomalacia, and one of these was also hypocalcaemic. Possible precipitating factors were rapid bone growth in three young patients, low dietary vitamin D intake in six, and cholestyramine therapy in one.

Two patients with severe osteomalacia showed histological improvement after one year of parenteral vitamin D<sub>2</sub> therapy. Two others with severe osteomalacia were treated with oral 1  $\alpha$ -hydroxy-vitamin D<sub>3</sub> and 25-hydroxyvitamin D<sub>3</sub> respectively; both showed a dramatic histological improvement after six months' treatment.

It is concluded that osteomalacia is common after small intestinal resection, and bone biopsy is essential for its diagnosis. Oral therapy with vitamin D metabolites or analogues can be effective and offers possible advantages over parenteral vitamin D therapy.

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#### STOMACH AND DUODENUM

#### Statistical analysis of experimental data: evaluation of some common errors with reference to gastric secretion studies

P. B. BOULOS, P. F. WHITFIELD, R. G. FABER, AND M. HOBSLEY (*Department of Surgical Studies, The Middlesex Hospital and Medical School, London*) The interpretation of numerical data usually depends upon statistical evaluation. The 'parametric' tests commonly used are valid only if the data are normally distributed.

Taking gastric secretion as an example, we have analysed the distributions of histamine and insulin stimulated acid output in 70 control subjects and 124 patients with duodenal ulcer. Only in some instances were the data normally distributed. For non-normal data non-parametric tests must be used unless the data can be transformed to a normal distribution. This, indeed, was possible in the examples quoted by taking the square-root of each value; the simple parametric tests could then be applied. The changed interpretations were often striking—for example, the lower boundry of maximal acid output in the control group was only 2.5 mmol/h by raw data, but 7.3 mmol/h after taking the square root.

It is well-known that gastric secretion is related to stature<sup>1</sup>. A method of standardisation is to express secretion per unit body stature<sup>2</sup>; however, regression analysis reveals that this method is rarely applicable. When data are normally distributed standardisation should be made by using the appropriate regression formula.

Application of these statistical considerations should improve the evaluation of experimental data, and allow fairer comparison between the results from different centres.

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#### Thiocyanate as a marker of saliva in gastric juice?

P. B. BOULOS, M. DAVE, P. F. WHITFIELD, AND M. HOBSLEY (*Department of Surgical Studies, The Middlesex Hospital and*



Medical School, London) Aspirated gastric juice contains thiocyanate<sup>1</sup>. It is known that there is thiocyanate in saliva, but generally accepted that there is none in pure gastric juice<sup>2</sup>. It is therefore possible that the thiocyanate in gastric juice can be used to monitor its content of swallowed saliva.

In 22 patients with duodenal ulcer, simultaneous oral- and gastric-aspiration was performed during basal, insulin-stimulated and histamine-stimulated secretion. In 60 (30%) of 198 10-minute sample-pairs, gastric juice thiocyanate concentration exceeded salivary thiocyanate. Moreover, when gastric secretion increased significantly ( $P < 0.01$ ) during histamine stimulation, there was no significant change in the gastric thiocyanate concentration.

These findings indicate that there must be a source of thiocyanate other than saliva in gastric aspirate. This source is probably gastric juice itself, although a contribution from duodenogastric reflux remains a possibility. Thus, thiocyanate cannot be used as a marker of salivary contamination of gastric juice.

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#### Vagotomy and intragastric acidity

R. F. MCCLOY, D. P. GIRVAN, AND J. H. BARON (*Department of Surgery, Royal Postgraduate Medical School and Hammer-smith Hospital, London*) Gastric acidity has recently been used to claim that efficacy of an antisecreting drug is comparable with vagotomy<sup>1</sup>, but little is known of the effect of gastric operations on intragastric pH<sup>2</sup>.

We studied the effect of truncal (TV) and selective vagotomy (SV) on intragastric pH in seven patients with duodenal ulcer, who were asymptomatic four years after operation.

Twenty-four hourly gastric aspirates were performed on two patients (one SV, one TV) immediately before, eight days, and four years after operation. The TV patient had 96% of pH samples  $< 2$  preoperatively and none  $< \text{pH } 2$  one week or four years after operation, with a 97% reduction in peak acid output (PAO). The SV patient had 41% of preoperative samples  $< \text{pH } 2$  and 4%  $< \text{pH } 2$  eight days

later with 69% reduction of PAO. After four years 21% of samples were  $< \text{pH } 2$  and PAO was reduced by only 20%.

Of three other patients, four years after TV, two had no pH samples  $< 3.5$  and PAO was reduced by 95 and 97%. The other patient had 29% of samples  $< \text{pH } 2$ , 86%  $< 3.5$ , and a 76% reduction in PAO.

Two other SV patients, four years after operation, had 68% and 71% of samples  $< \text{pH } 2$  and the latter a PAO reduction of 75%.

There was a significant correlation of intragastric acidity with basal, insulin, and pentagastrin stimulated acid output. Thus, in the treatment of duodenal ulcer, intragastric acidity may be less important than the amount of acid entering the duodenum.

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#### A non-invasive test of gastric function

T. V. TAYLOR, D. BONE, AND BRUCE TORRANCE (*Royal Infirmary, Manchester*) The gastric secretion of the  $\gamma$  emitting radioisotope <sup>99m</sup>technetium in response to pentagastrin, histamine, and betazole has been shown to correlate closely with acid secretion using an invasive technique<sup>1,2,3</sup>.

Fifty patients had their maximal secretory capacity determined in response to pentagastrin (6  $\mu\text{g}/\text{kg}$ ) using a  $\gamma$ -camera and a non-invasive technique. After 15 minutes <sup>99m</sup>Tc (1 m.Ci intravenously) was given and gastric scans were taken for 30 minutes and the intragastric activity was determined after subtraction of background.

After total gastrectomy no discrete image was formed with no fall-off of background activity, indicating that the stomach was the only appreciable source of <sup>99m</sup>Tc concentration. Pernicious anaemia patients had intragastric counts only marginally above background. Twelve duodenal ulcer patients all showed a reduction in activity after vagotomy (mean reduction 48.4%,  $P < 0.0005$ ). The mean concentration in duodenal ulcer patients was 44.2% higher than in normal subjects ( $P < 0.05$ ) and 68.4% higher than in the gastric ulcer and carcinoma groups combined ( $P < 0.0025$ ). Hiatus hernia, reflux oesophagitis, and Meckel's diverticula can be diagnosed using this test.

This non-invasive test of gastric function provides a convenient method of assessing a parameter of gastric function proportional to acid output. It is extremely accurate and produces no discomfort, losses due to gastric emptying and pooling of secretions being overcome. The dose of isotope is 10% that used in a routine brain scan.

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#### Failure to detect back-diffusion in human gastric aspirate

P. F. WHITFIELD AND M. HOBSELY (*The Department of Surgical Studies, The Middlesex Hospital and Medical School, London*) One explanation for the presence of sodium ions in gastric juice is that hydrogen ions in the secreted hydrochloric acid are exchanged one-for-one with sodium ions through the gastric mucosa ('back diffusion')<sup>1</sup>.

During steady-state gastric secretion (verified by continuous instillation of a marker, phenol red)<sup>2</sup>, the volumes of consecutive aspirated samples may vary. Episodic sequestration of portions of the stomach contents results in a smaller aspirate, to be succeeded in the next collection-period by a larger than average volume. Post-sequestration samples contain juice that has been in contact with the stomach mucosa longer than aspirate during the period of sequestration. They might therefore be expected to display the characteristics of back-diffusion more clearly.

During  $\frac{1}{4}$ -maximal and maximally-stimulated<sup>3</sup> steady-state gastric secretion, 47 pairs of sequestration/post-sequestration samples were identified and their Na and H concentration compared. The differences,  $\Delta [\text{Na}]$  and  $\Delta [\text{H}]$  were examined by linear regression. The slope  $\Delta [\text{H}]$  (y) vs  $\Delta [\text{Na}]$  (x) was  $-1.5$  ( $r = -0.88$ ,  $P < 0.001$ ). By the back-diffusion hypothesis, this slope should have been  $-1.0$ . However,  $-1.5$  is consistent with contamination of gastric juice by duodenogastric reflux.

Thus, during stimulated secretion, back-

diffusion is undetectable, but duodeno-gastric reflux is a plausible source of sodium in gastric juice.

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### Does acid back diffusion and dilution reduce the concentration of acid secreted by the parietal cell?

M. R. THOMPSON AND M. GIPSMAN (*Department of Surgery, Manchester Royal Infirmary, and V. A. Centre, Wadsworth Hospital, Los Angeles*) Acid back diffusion<sup>1</sup> and neutralisation<sup>2</sup> are possible explanations for the variation in acid concentration of gastric juice. Both these mechanisms will result in a decrease in the osmolarity of the acid. In order to determine whether these two hypotheses are correct HCl at three concentrations (50, 100, and 150 mM made isotonic with mannitol) was instilled into gastric pouches of four cats and net H<sup>+</sup>, Na<sup>+</sup> and Cl<sup>-</sup> fluxes, net volume output, and change in osmolarity were measured in the usual way<sup>3</sup>.

Increasing the concentration of acid instilled significantly increased ( $p < 0.05$ ) net H<sup>+</sup> loss (-27, -75 and -131  $\mu\text{Eq}/30$  min), net Na<sup>+</sup> gain (+214, +268 and +294  $\mu\text{Eq}/30$  min), net volume output (+0.5, 0.9 and 1.2 ml/30 min), and the change in osmolarity was +12, +3 and -10 mosmol/l/30 min respectively. These data are compatible with either theory<sup>1,2</sup>.

The crucial factor determining which is correct is the nature of the increase in fluid output. In further experiments the increase in fluid output stimulated by 150 mM HCl continued during the subsequent instillation of 5 mM HCl. During this time the increase in Na<sup>+</sup> output was matched by an increase in Cl<sup>-</sup> output (+138  $\mu\text{Eq}$  Na<sup>+</sup> and +184  $\mu\text{Eq}$  Cl<sup>-</sup>). Therefore the decrease in osmolarity is due to HCl back diffusion and the increase in Na<sup>+</sup> output is due to the secretion of a solution of NaCl.

Thus, acid concentration was reduced by H<sup>+</sup> back diffusion and dilution with a solution of NaCl.

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### Effect of the histamine H<sub>2</sub> antagonist cimetidine on gastric mucosal blood flow

S. E. KNIGHT, R. L. MCISAAC, AND L. P. FIELDING (H. A. F. DUDLEY) (*Academic Surgical Unit and Department of Physiology, St. Mary's Hospital Medical School, London*) Cimetidine is effective in reducing blood loss in patients with haemorrhagic gastritis caused by liver failure<sup>1</sup>. This might be due partly to a direct action on the gastric microvasculature. To investigate this aspect we determined gastric mucosal blood flow (GMBF) change in response to cimetidine in six volunteers; using neutral red (NR) clearance to estimate GMBF<sup>2</sup>.

After nasogastric intubation each subject received NR (250  $\mu\text{gkg}^{-1}\text{h}^{-1}$ ) intravenously by constant infusion. Gastric juice (15 min aliquots) and blood (30 min samples) were collected. After three basal samples pentagastrin (6  $\mu\text{gkg}^{-1}\text{h}^{-1}$ ) was infused intravenously. When acid production had reached a plateau, cimetidine (2  $\text{mgkg}^{-1}\text{h}^{-1}$ ) was given intravenously for 30 minutes. NR was extracted from blood and gastric juice with the non-polar solvent ether and estimated spectrophotometrically at 540 nm.

The main result was that cimetidine halved gastric mucosal blood flow. Acid output was also reduced but the ratio of GMBF to acid output remained constant.

We conclude that the action of cimetidine in reducing blood flow through the gastric mucosa may help to explain this drug's beneficial effect in bleeding erosive gastritis.

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### Effect of prolonged metiamide medication on acid secretory capacity and gastrin sensitivity of the rat parietal cell

F. HALTER, W. H. HÄCKI, S. K. HÄCKI, AND

L. WITZEL (introduced by W. SIRCUS) (*Gastrointestinal Unit, University Hospital Inselspital, Bern, Switzerland*) The increase in acid secretion observed in the rat after cessation of prolonged treatment with high doses of metiamide<sup>1</sup> is greater than expected from the gain in parietal cell mass<sup>2</sup>. Using a perfused rat stomach preparation<sup>3</sup> the gastrin dose-response relationship was therefore compared in metiamide and placebo treated animals.

Groups of 10 rats each were subcutaneously injected during three weeks with 200 mg/kg metiamide alone (group I) or in combination with 200 mg atropine (II) at eight-hourly intervals. Controls were given atropine or saline.

In acute experiments metiamide led to prolonged (up to four-fold) rise in serum gastrin, which was suppressed by atropine. From the acid secretory response to graded doses of HG 17 I, 12 hours after the last medication, the calculated maximal acid secretory capacity ( $V_{\text{max}}$ ) and the ED 50 were established. In both metiamide treated groups (I + II)  $V_{\text{max}}$  was twofold higher and the ED 50 only half that in both control groups ( $p < 0.001$ ).

Thus, in the rat, prolonged metiamide medication increases gastrin-sensitivity and maximum secretory capacity of the parietal cell and endogenous hypergastrinaemia seems not to be the prime mediator.

These results underline the necessity of differentiated acid secretory studies in patients subjected to long term histamine H<sub>2</sub>-antagonist treatment.

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### Is intrinsic factor really affected by cimetidine?

P. C. SHARPE, M. A. HORTON, R. H. HUNT, JANE G. MILLS, S. H. VINCENT, AND G. J. MILTON-THOMPSON (*Royal Naval Hospital, Haslar, Hampshire; Clinical Research Department, Smith Kline and French Laboratories Ltd.; Department of Haematology, St. Bartholomew's Hospital, Lon-*

don) Controversy exists as to the extent to which cimetidine reduces output and concentration of intrinsic factor (IF)<sup>1,2</sup>.

In order further to evaluate the effects of cimetidine, seven healthy males were studied on three occasions. On day 1 cimetidine 100 mg/h was infused intravenously for 135 minutes with simultaneous infusion of pentagastrin (PG) for the last 90 minutes. On day 2 PG alone was infused for 90 minutes. On completion, cimetidine 200 mg intravenously was given followed by 2 g/day for one week, when the procedure of day 1 was repeated. Gastric aspirates were analysed for acidity and IF concentration.

Similar results were obtained on days 1 and 3. Compared with day 2, mean peak IF output on days 1 and 3 were reduced by 49% ( $P < 0.05$ ) and 41% ( $P < 0.01$ ) respectively, while total output after PG was reduced by 37% ( $P < 0.01$ ) on day 1 and by 30% (NS) on day 3. No effect was seen on IF concentration on either study day 1 or 3 or on the time course of the response. Mean acid output on days 1 and 3 was reduced by 70% and 58%, acidity by 45% and 35%, and volume by 45% and 35% respectively.

Peak IF output was significantly reduced, but this effect was related to the reduction in volume of gastric aspirates. We conclude that treatment with high doses of cimetidine for one week does not affect IF response and that synthesis of IF is probably not altered by cimetidine.

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#### Effect of one year's treatment with cimetidine on fasting and Oxo-stimulated serum gastrin in duodenal ulcer patients

R. W. SPENCE, L. R. CELESTIN, D. A. MCCORMICK, C. J. OWENS, AND J. M. OLIVER (Department of Gastroenterology, Frenchay Hospital, Bristol; University Departments of Surgery and Medicine, Bristol Royal Infirmary) Twenty-three duodenal ulcer patients have completed one year's treatment with cimetidine 1.6 g daily. Previously we reported the effect of three months' treatment on fasting and Oxo-stimulated serum gastrin concentra-

tions in 22 of these patients<sup>1</sup> when no changes in serum gastrin were found in 18 patients but in four patients marked increases in fasting and stimulated concentrations were recorded associated with resting intragastric pH values of  $> 6.0$ . An identical Oxo test was performed in each patient after completion of one year's treatment ( $51.4 \pm 1.3$  weeks) in which the test solution was instilled through a Ryle's tube, samples of gastric juice were aspirated for measurement of pH and H<sup>+</sup> concentration, and venous blood samples were withdrawn for radioimmunoassay of their gastrin content. The integrated gastrin response (IGR) was calculated by the method described by Ganguli *et al.* (1974)<sup>2</sup>.

Results before treatment and after three and 12 months were compared using a Wilcoxon matched-pairs signed-ranks test. At one year both peak gastrin concentrations and IGR were significantly increased compared with both pre-treatment and three month values ( $P < 0.01$  in every case) but fasting gastrin concentrations were not significantly altered. Compared with pre-treatment values, all patients except one showed an increased IGR at one year. However, stimulated serum gastrin concentrations  $> 1000$  ng/l were found in only three patients and this change had occurred in the first three months of treatment in these patients. All patients except one had a resting intragastric pH of  $< 2.0$  immediately before the one year test. Mean serum gastrin concentration (ng/l)  $\pm$  SDs pre-treatment, at three months and one year respectively were; fasting  $63 \pm 27$ ,  $102 \pm 149$ ,  $85 \pm 88$ ; peak  $259 \pm 167$ ,  $459 \pm 566$ ,  $608 \pm 481$ ; IGR (pg)  $562 \pm 471$ ,  $1041 \pm 1478$ ,  $1649 \pm 1326$ .

One year's treatment with cimetidine has therefore produced an approximately three-fold increase in the serum gastrin response to Oxo (IGR) in this group of patients. This has not resulted in a rebound of acid secretion on discontinuation of treatment nor in an increased severity of symptoms in the two patients who have relapsed to date.

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#### Long-term effects of cimetidine on gastric secretion

R. J. HOLDEN, J. B. HEARNS, B. MCKIBBEN, K. B. BUCHANAN, AND G. P. CREAM (The Gastrointestinal Centre, Southern General Hospital, and the University Department of Medicine, Queen's University, Belfast) Gastric secretion and serum gastrin levels were studied serially before, during and after prolonged treatment with cimetidine. Patients with duodenal ulceration were randomly allocated to treatment with 800 mg cimetidine daily ( $n = 6$ ) or 1600 mg daily ( $n = 6$ ) for eight weeks; tests were carried out in the week before starting treatment, at weeks 1, 2, 4, and 8 of treatment, and at weeks 1, 2, and 4 after treatment had ceased. Acid and pepsin outputs were determined from the results obtained in the first hour after 'maximal' pentagastrin stimulation; serum gastrin levels were determined from samples taken in the fasting state. Acid and pepsin outputs were both significantly decreased during the treatment period; however, while acid output tended to return to control levels after treatment had ceased, pepsin output did not. The higher dose of cimetidine exerted significantly greater effects on acid secretion than did the lower dose, but there were no significant dose effects with respect to pepsin secretion. There was no cumulative effect on acid or pepsin secretion with time, at either dose level. There were no significant changes in serum gastrin levels throughout.

#### Effect of ionic strength on the proteolytic characteristics of human pepsins

I. M. SAMLOFF AND V. DADUFALZA (Department of Medicine, Harbor General Hospital and UCLA School of Medicine, Los Angeles) (introduced by J. B. ELDER) The proteolytic characteristics of animal and fish pepsins are altered by changes in the ionic strength of the incubation mixture<sup>1,2</sup>. This study examines the effect of ionic strength on the proteolytic characteristics of human pepsin I (PN I) and pepsin II (PN II) against human haemoglobin. The apparent pH optima of PN I and PN II were about 2.2 and 3.4 when the ionic strength of the assay mixture was determined solely by the concentration of HCl required to obtain a pH gradient of 1 to 5. The addition of NaCl to maintain ionic



strength constant at 0.15 resulted in a shift in the pH optimum of PN II to 2.5 and an almost two-fold increase in its specific activity ( $\Delta$  absorbance 280 nm/ $\mu$ g enzyme). The effects of PN I were minor. At ionic strength 0.025, the ratio of PN I to PN II in a mixture had little effect on proteolytic activity. In contrast, at ionic strength 0.15, proteolytic activity increased progressively as the ratio of PN I to PN II in the mixture decreased. Studies of gastric juice paralleled the changes found for PN I and PN II. The results indicate that the pH optima of PN I and PN II are similar when ionic strength is maintained at a physiological level, that the specific activity of PN II is almost twice that of PN I, and that the peptic activity of gastric juice is determined not only by pH and total pepsin concentration, but also by ionic strength and the ratio of PN I to PN II.

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#### Mechanism of action of metoclopramide: importance of intrinsic sources of acetylcholine

A. M. HAY, W. K. MAN, AND R. F. MCCLOY (introduced by Professor R. B. WELBOURN) (*Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London*) Recently published data<sup>1,2</sup> from this laboratory suggest that metoclopramide enhances the contractile activity of the guinea-pig antrum by increasing acetylcholine release from the post-ganglionic cholinergic nerve ending.

Further studies with longitudinal muscle strips prepared from guinea-pig antrum have revealed an inhibitory interaction between metoclopramide and anticholinesterase, making conventional techniques for the measurement of acetylcholine release inappropriate. We have, therefore, used an indirect approach to test our hypothesis.

Muscle strips were stimulated repetitively (200  $\mu$ s pulses, 20 Hz, supra-maximal current) for two hours in the presence of hemicholinium-3 (200  $\mu$ M). Pre-treatment in this manner produced a mean reduction of 50% in the acetylcholine pool size, when compared with that in stimulated control strips not

incubated with hemicholinium-3. In the hemicholinium-treated strips there was complete abolition of the normal excitatory response to metoclopramide (110  $\mu$ M). Only a small reduction in this response was detected in strips which were incubated with hemicholinium-3 but not stimulated, and in which there was no significant change in acetylcholine pool size.

The stimulant effect of metoclopramide depends, therefore, upon maintenance of intrinsic stores of acetylcholine. This finding lends further support to the hypothesis of increased acetylcholine release.

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#### Bile reflux and gastric emptying in patients with combined ulcer disease

M. J. GOUGH, C. S. HUMPHREY, D. B. FEATHER, AND G. R. GILES (*University Department of Surgery, St. James's University Hospital, Leeds*) The presence of a gastric ulcer in a patient with duodenal ulceration is usually attributed to gastro-duodenal reflux and gastric stasis. To investigate this problem we have studied eight patients with combined ulceration (DU + GU). The bile content of gastric juice was measured under basal conditions and during maximal pentagastrin stimulation and the severity of any gastritis assessed by the back-diffusion technique. Gastric emptying of a 5% glucose meal was estimated by the George dye dilution technique. The results have been compared with similar studies in 17 patients with uncomplicated duodenal ulcer (DU).

Basal and peak acid outputs were similar in both groups. It was only possible to detect bile in the basal secretion of two patients with DU + GU and four patients with DU. After pentagastrin bile reflux occurred in three patients with DU + GU compared with seven patients with DU. The mean net loss of H<sup>+</sup> ions during acid instillation was 1.66 mmol H<sup>+</sup>/15 min (-1.19 to 3.67) in the DU + GU patients and 1.99 mmol H<sup>+</sup>/15 min (0.20 to 3.52) in the DU group. The mean half-life of the glucose meal was 20.9 minutes (-1 to 32) in DU + GU patients and 18.6 minutes (8 to 43) in DU patients.

These studies failed to show any

differences in gastro-duodenal reflux and gastric emptying between the two groups of patients.

#### Effects of proximal gastric vagotomy and truncal vagotomy and antrectomy on gastritis, bile reflux, and acid output

A. M. HOARE, I. DONOVAN, AND J. ALEXANDER-WILLIAMS (*The Queen Elizabeth and General Hospitals, Birmingham*) A randomised trial has been performed comparing proximal gastric vagotomy (PGV) with truncal vagotomy and antrectomy (TV and A) in 71 patients with duodenal ulcer. Twelve months later endoscopy with gastric biopsies and a pentagastrin test, including measurement of bile acids in the fasting aspirate<sup>1</sup>, were performed. Thirty-five patients had PGV and 36 TV and A, of whom 58 volunteered for postoperative endoscopy and 46 for pentagastrin test.

Bile reflux was less after PGV than TV and A ( $P < 0.05$ ). After TV and A six patients had more than 120  $\mu$ mol/h reflux of bile acids, and all had symptoms. All patients with more than 40  $\mu$ mol/h bile reflux had gastric erythema on endoscopy.

Gastritis of the distal stomach was more common after PGV, but was found in the proximal stomach equally commonly after both operations. It was unrelated to bile reflux or symptoms. Five duodenal ulcers were found after PGV, but had peak acid output (PAO) greater than 20 mmol/h and normal mucosa proximally. No ulcers were found after TV and A, but PAO greater than 15 mmol/h was associated with a normal mucosa proximally ( $P > 0.02$ ). Successful reduction of acid output by ulcer surgery appears to be associated with the development of gastritis.

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#### Are prostaglandins deficient in peptic ulceration?

R. BAKER, B. M. JAFFE, J. D. REED, B. SHAW, AND C. W. VENABLES (*Departments of Surgery and Physiology, University of Newcastle upon Tyne, and Washington University, St. Louis, Missouri, USA*) It has been previously shown, in animal studies, that there is a positive correlation between gastric acid and PGE and PGF secretion<sup>1</sup>. As duodenal ulceration is associated with

hypersecretion, it might be expected that changes in plasma PGE and PGF could occur in this disease. Fasting plasma levels of PGE and PGF were measured, by radioimmunoassay<sup>2</sup>, in 100 patients undergoing diagnostic upper gastrointestinal endoscopy. These patients were categorised into four diagnostic groups.

It was found that active duodenal ulceration was associated with a significantly raised mean PGE level when compared with the other groups ( $P < 0.01$ ). Plasma PGF did not differ significantly between the various groups. There was wide individual variation in PGE and PGF levels.

Plasma PGE and PGF did not alter significantly in 21 patients treated with cimetidine 400 mg q.d.s. for 28 days irrespective of the success, or otherwise, of therapy.

In duodenal ulcer patients no correlation was found between plasma PGE and basal acid output (14 patients), plasma PGE and stimulated acid output (17 patients), or plasma PGE and serum gastrin (13 patients). Gastric juice PGE output correlated with acid output ( $r = 0.563$ ,  $P = 0.001$ ), but not with pepsin output (five patients), confirming our animal studies.

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#### LIVER AND BILIARY

### Bran and bile: time-course of changes in normal young men given a standard dose

K. W. HEATON AND A. C. B. WICKS (*University Department of Medicine, Bristol Royal Infirmary, Bristol*) Previously, we have shown that bran feeding causes significant changes in bile acid composition and metabolism, and an improved cholesterol saturation of bile in gallstone patients<sup>1,2</sup>. These studies used various doses of bran and a single sampling time at four to six weeks. We have now fed a standard dose of bran (15 g twice daily) to 12 healthy young men, and analysed duodenal bile after one, two, four, and six weeks. At six weeks, but not earlier, there was a reduction in deoxycholate, from  $22.7 \pm$

$2.8$  to  $16.5 \pm 1.8\%$  (mean  $\pm$  SEM,  $P < 0.01$ ) and an increase in chenodeoxycholate, from  $30.1 \pm 1.6$  to  $34.9 \pm 2.2\%$  ( $P < 0.01$ ), the changes being the same as observed previously. Bile was unsaturated with cholesterol at the beginning and remained so throughout. The glycine/taurine conjugation ratio, body weight, and plasma lipids were unchanged.

The delay in the action of bran suggests that its primary effect is to reduce the formation of deoxycholate, rather than merely to impede its absorption by physically altering the stools.

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### Bile acid, neutral sterol, and faecal fat excretion in subjects treated with fenfluramine

M. S. SIAN AND A. J. HARDING RAINS (*Professorial Department of Surgery, Charing Cross Hospital Medical School, London*) In view of the excessive wastage of bile salts during the diarrhoea after treatment with fenfluramine, we have studied bile acids, neutral sterols, and faecal fat excretion in 16 healthy subjects before, during, and after administration of fenfluramine.

Analysis of variance revealed a statistically significant increase in bile acid excretion during the drug phase ( $P < 0.01$ ) and during recovery ( $P < 0.01$ ). Excretion during pre-drug, drug, and recovery phase was 9.537, 12.766, and 12.032 mg/g dry wt. faeces. Increased neutral sterol excretion coincided with bile acid elimination. There was a lack of correlation between faecal fat and drug administration, and in the three subjects with diarrhoea faecal fat and bile acid loss was markedly reduced; bile acids excreted were mainly chenodeoxy and cholic together with cholesterol as the main neutral sterol instead of coprostanol. This is evidence of reduced 7  $\alpha$  dehydroxylation in subjects with diarrhoea. Primary bile acids have been reported to induce watery diarrhoea in canine colon<sup>1</sup>.

Augmented bile acid and neutral sterol excretion as reported in this study is in agreement with the previous observation

made from this laboratory<sup>2</sup>, that fenfluramine caused a small but significant decrease in serum cholesterol; and another report which demonstrated 14% decrease in two weeks<sup>3</sup>.

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### Natural history of chronic persistent hepatitis

R. G. CHADWICK, J. GALIZZI, E. J. HEATHCOTE, B. COHEN, P. J. SCHEUER, AND S. SHERLOCK (*Academic Department of Medicine, Royal Free Hospital, London, and the Virus Reference Laboratory, Colindale Avenue, London*) Twenty-six patients (23 men and three women) with chronic persistent hepatitis (CPH) have been studied prospectively, clinically and by serial liver biopsies for six to 192 months (mean 48 months). In 16 there was evidence of past hepatitis B virus (HBV) infection. The aetiology of the others was unknown. Liver biopsies showed that in 15 CPH continued, while in three it resolved. Eight developed a mild chronic active hepatitis (CAH). These latter patients had often presented insidiously and were symptom-free; a rise in serum transaminase was the only abnormality. None developed cirrhosis.

'e' antigen was present in only one of the 15 HBsAg positive patients and this subject progressed to CAH. Serum antibodies against nuclei, mitochondria, and smooth muscle were not detected.

It is concluded that CPH is a benign condition, predominantly affecting men, which may follow HBV infection. 'e' is usually absent. CAH developed in eight of 26 patients, more often in those presenting insidiously, but this was mild and non-progressive. Cirrhosis was not a sequel.

### Chronic lobular hepatitis: a distinct entity?

S. P. WILKINSON, B. PORTMANN, A. M. G. COCHRANE, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London*) Three adult male patients described here presented with the

characteristic clinical history and biochemical changes of an acute viral hepatitis, but antinuclear factor was invariably positive (>1:160) and one patient also had a Coomb's-positive haemolytic anaemia. HBsAg was negative. Initial liver biopsy was indistinguishable from acute hepatitis—namely, an acute inflammatory infiltrate throughout the lobules with relatively little change in the portal areas. After two to five months' observation, when the illness showed no signs of remitting, corticosteroids were given with rapid symptomatic and biochemical improvement.

During follow-up for three, three, and eight years attempts to reduce prednisone dosage below 17.5 mg/day invariably resulted in reappearance of deep jaundice and strikingly high values of AST (500 to 2000 IU/l). Further biopsies during remission have shown a complete return to normal, but during relapse the changes have always been those initially observed with the inflammatory infiltrate confined largely to the lobules ('lobular hepatitis'), without progression to cirrhosis even after eight years in one patient. One patient has subsequently died after a staphylococcal septicaemia.

These cases, it is suggested, represent a distinct entity, with histological features of acute viral hepatitis, but clinical and immunological features more in keeping with chronic active hepatitis, in that long-term corticosteroid therapy seems essential, although progression to that disease has not been observed, and the term chronic lobular hepatitis is a suitable descriptive one.

#### Treatment of HBsAg-positive chronic active hepatitis with human fibroblast interferon

J. G. C. KINGHAM, N. K. GANGULY, Z. D. SHAARI, S. T. HOLGATE, M. J. MCGUIRE, R. MENDELSON, T. CARTWRIGHT, G. M. SCOTT, B. M. RICHARDS, AND RALPH WRIGHT (*Professorial Medical Unit, Southampton General Hospital, Southampton and Searle Research Laboratories, High Wycombe*) Two patients with HBsAg positive chronic active hepatitis have been treated with human fibroblast interferon 10<sup>7</sup>U daily for two weeks. Serum hepatitis B markers, DNA binding antibodies, liver function tests, and haematological parameters have been tested before, during, and for four months after treatment. Before treatment both patients had high levels of HBsAg and core antibodies (anti-HBc) and high

DNA binding antibodies; in one patient there was a fourfold rise in the serum AST. During treatment there was a striking fall in the anti-HBc titre, which has been maintained; in one patient the initially high AST level fell to normal. In both patients high DNA binding antibodies fell during treatment to normal levels, which have been maintained.

The fall in titre of anti-HBc and DNA binding antibodies as a result of interferon treatment has several possible explanations: the release of core antigen and DNA, either autologous or viral specific from the liver, may complex with their respective antibodies resulting in a fall in titre. Alternatively, interferon treatment may stop viral replication in the liver with suppression of these markers.

No significant adverse effect occurred and these observations should encourage further trials of fibroblast interferon in hepatitis B.

#### Controlled trial of cyclophosphamide in active chronic hepatitis

I. T. GILMORE, R. E. COWAN, A. T. R. AXON, AND R. P. H. THOMPSON (*Gastrointestinal Laboratory, Rayne Institute, St. Thomas' Hospital, London*) Azathioprine is an accepted adjunct to corticosteroid treatment in active chronic hepatitis (ACH), but the value of other immunosuppressive agents is uncertain. In a controlled cross-over trial, cyclophosphamide has therefore been added to prednisolone therapy in patients with histologically confirmed HBsAg-negative ACH.

Activity of the disease was first kept under control (SGOT <2 × normal) for at least four weeks with prednisolone, which was then reduced every two weeks by 2 mg/day until relapse (SGOT >3 × normal). Prednisolone was then increased until control had been regained for four weeks, and the patients then randomly allocated to receive either cyclophosphamide, 2 mg/kg/day, or placebo for 12 weeks, while prednisolone was again reduced. After relapse prednisolone was increased, and, after four weeks' control, the patients were crossed over.

Ten patients entered the trial; five patients crossed over once and one twice, providing seven pairs of data for comparison (four patients failed to relapse). In four, a longer control period followed cyclophosphamide therapy than placebo, two patients having remissions for three to six months, but in two a longer control period followed placebo, and in one there

was no difference. All patients developed alopecia while taking cyclophosphamide, one haemorrhagic cystitis, three leucopenia, and the only male patient developed azospermia.

Therefore we doubt that cyclophosphamide aids the management of ACH sufficiently to justify its toxicity, and the trial has been concluded.

#### Serial changes in plasma tyrosine and phenylalanine levels in patients with fulminant hepatic failure treated by polyacrylonitrile haemodialysis: relationship to coma

R. A. CHASE, M. DAVIES, P. N. TREWBY, D. B. A. SILK, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London*) Previous work in experimental hepatic coma has suggested a causal relationship between rises in levels of plasma tyrosine and phenylalanine and accumulation in the brain of the false neurotransmitters, octopamine and phenylethanolamine<sup>1</sup>. In the present study we have therefore examined serial changes (two to six hourly) in plasma amino acid profiles of 26 patients with fulminant hepatic failure treated by daily four to six hours polyacrylonitrile haemodialysis<sup>2</sup>, of whom 10 regained consciousness and nine (34.6%) survived.

Plasma levels of tyrosine (median 270.5 μM, range 78-573) and phenylalanine (318 μM, range 77-716) were raised three- to four-fold above normal controls on admission in grade IV coma. Clearances equivalent to nine pretreatment pools of these amino acids were achieved during six hour haemodialysis, indicating the rapidity with which they re-equilibrated between tissue and plasma compartments.

Despite removal of large quantities (5.17 mmol tyrosine, 2.81 mmol phenylalanine) of amino acids during six hour dialysis, there was no relationship between total removal and final outcome. Serial studies in six survivors showed plasma levels returning to normal 48 hours in advance of recovery of consciousness in four out of six patients (phenylalanine) and three out of six (tyrosine).

This inexact relationship suggests that raised plasma levels of tyrosine and phenylalanine are *not* solely responsible for the encephalopathy in fulminant hepatic failure.

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### Insulin, glucagon, and amino acid imbalances in fulminant hepatic failure

R. A. CHASE, S. SULLIVAN, S. R. BLOOM, D. B. A. SILK, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London, and Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London*) Hepatic encephalopathy in patients with chronic liver disease is associated with changes in plasma amino acid patterns—decreased branched chain amino acids (valine, leucine, isoleucine) and increased aromatic amino acids (phenylalanine, tyrosine)<sup>1</sup> mediated, it is suggested, by a reduction of the molar ratio of immunoreactive insulin to glucagon from 3 to 1<sup>2</sup>.

These relationships were the subject of the present study in 25 patients with fulminant hepatic failure in grade IV coma. Branched chain amino acids (BCAA) ( $354.9 \pm SE 38.0 \mu\text{mol/l}$ ) were normal. Aromatic amino acids (AAA) were increased three-fold ( $538.7 \pm 50.0$ ), so that the ratio BCAA/AAA was reduced ( $0.74 \pm 0.08$  compared with  $3.29 \pm 0.26$  in controls). Insulin ( $1094 \pm 285 \text{ pmol/l}$ ) and glucagon ( $74.6 \pm 10.6 \text{ pmol/l}$ ) were both markedly raised and the mean insulin/glucagon ratio was 22.2. Repeat measurements in four patients as conscious level improved (grades 0-II coma) showed that there was a fall in both insulin (mean 22.3%) and glucagon (49.8%). The mean insulin/glucagon ratio remained raised (10.7), however, and the BCAA/AAA ratio ( $0.96 \pm 0.13$ ) was still markedly reduced.

These findings strongly suggest that, unlike the situation in the encephalopathy of chronic liver disease, the amino acid changes in FHF are *not* caused by reductions in the insulin/glucagon ratio.

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### Loss of cerebral autoregulation in an animal model of liver failure

P. N. TREWBY, M. A. HANID, R. L. MACKENZIE, P. J. MELLON, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London*) Two main complications of fulminant hepatic failure are hypotension and cerebral oedema developing in association with a raised intracranial pressure. Little is known as to the relationship between these two and cerebral blood flow and we have therefore investigated this in a pig model of surgically induced acute liver failure.

When normotensive (systolic BP 90-120 mmHg) cerebral blood flow (CBF) was significantly lower in the animals with liver failure than in the controls. Induction of hypotension was associated with a further fall, a significant positive correlation being found between CBF and systolic BP in the animals with liver failure ( $r = 0.53$ ,  $P < 0.01$ ). In the controls no such fall in CBF occurred despite systolic blood pressures of as low as 30 mmHg. In the animals with liver failure but not in the controls a raised intracranial pressure further compounded the fall in CBF.

As CBF fell there was a significant fall in cerebral metabolic rate for oxygen ( $\text{CMRO}_2$ ) in the animals with liver failure, whereas in the controls a fall in CBF was accompanied by a compensatory increase in oxygen extraction so maintaining a normal  $\text{CMRO}_2$ .

This disruption in cerebral circulatory responses, if extrapolated to man, emphasises the importance of preventing the rise in intracranial pressure consequent on cerebral oedema, and promptly treating any reduction in blood pressure if secondary hypoxic brain damage is to be avoided.

### Study of interobserver variation between liver histopathologists

A. THEODOSSI, R. P. KNILL-JONES, D. B. A. SILK, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital, Denmark Hill, London*) Relatively little information is available about interobserver variation between histopathologists, and the purpose of the present study was to assess the magnitude of such variation among two experienced and one senior trainee histopathologist. Without knowledge of the diagnosis, each reviewed the same 60 specimens obtained from patients with acute viral hepatitis (22), alcoholic cir-

rhosis (20), and extrahepatic bile duct obstruction (18), and completed coding forms which listed 18 hepatocyte and eight portal tract abnormalities graded 1-4 depending on severity.

With respect to diagnosis, there was agreement between the two experienced observers in 48 of 60 (80%) cases. However, total agreement among all three was less (56.7%). Agreement regarding specific histological abnormalities was uniformly distributed among the three observer pairs and occurred in 62.5% of the 4534 comparisons. Minor disagreement (one grade differences) occurred in 26.4% of comparisons. Differences of two grades occurred in 10.9% of comparisons but severe disagreement (three grade differences) occurred in only 0.2% of comparisons.

Although the results showing complete agreement about grading of specific histological abnormalities in two-thirds of cases are reassuring, with regard to reaching a final histological diagnosis, experience appears to be of more major importance.

### Histochemical demonstration of liver copper and copper carrying protein in chronic liver disease

S. JAIN, P. J. SCHEUER, BARBARA ARCHER, S. NEWMAN, AND SHEILA SHERLOCK (*Departments of Medicine, Histopathology, and Physics, Royal Free Hospital, Pond Street, London*) Liver copper concentrations can be raised in most chronic liver diseases. In Wilson's disease removal of excess copper by chelation is essential, and the same treatment may be of use in primary biliary cirrhosis<sup>1</sup> (PBC). Liver copper concentrations have been measured by neutron activation analysis, and compared with staining for copper by rubeanic acid and rhodanine, and with copper-carrying protein stained by orcein<sup>2</sup>. The comparison has been made in 69 percutaneous liver biopsies; 35 patients had PBC, 18 Wilson's disease, and 16 chronic active hepatitis (CAH), HBsAg positive and negative. Liver copper concentrations were raised in 31 of the patients with PBC, and the degree of histochemical staining for copper (graded 0-3) rose with increasing liver copper levels. Orcein staining was positive in 33 of the 35 patients.

All of the patients with Wilson's disease had high liver copper concentrations, but nine of the 18 had negative histochemical staining for copper, and 12 were orcein

negative. Similarly, histochemical stains gave little indication of the liver copper concentration in CAH. Histochemical staining of liver sections is useful in detecting rises in liver copper in PBC, but not in Wilson's disease, where the absolute concentration must be measured.

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#### Value of serum ferritin in the management of haemochromatosis

R. G. BATEY, S. HUSSEIN, SHEILA SHERLOCK, AND A. V. HOFFBRAND (*Department of Medicine and Haematology, Royal Free Hospital, Hampstead, London*) The role of serum ferritin (FN) in diagnosing haemochromatosis is currently being questioned<sup>1</sup> as FN metabolism may be abnormal in this disease<sup>2</sup>.

We have assessed the value of the test at diagnosis during venesection therapy and during iron reaccumulation and report these results. Liver biopsy iron has been taken as the final determinant of storage iron levels.

At diagnosis there was no correlation between FN and liver biopsy iron ( $n = 14$ ,  $P > 0.1$ ). The FN/aspartate transaminase ratio<sup>3</sup> correlated with liver iron values  $> 1000 \mu\text{g Fe}/100 \text{ mg liver}$  (normal  $< 160 \mu\text{g}/100 \text{ mg}$ ) but when liver iron was between  $160-1000 \mu\text{g}/100 \text{ mg}$  there was no correlation ( $r = 0.07$ ). Venesection resulted in an initial transient rise in FN values in two of eight patients but was followed in all by a progressive fall in values during therapy. No day-to-day or diurnal variation was noted in any patient. FN reached iron deficient levels before iron stores had been depleted in three out of five patients.

After venesection, FN remained low despite iron reaccumulation in two out of five.

Serum ferritin is of limited value in the management of haemochromatosis. It may aid in monitoring venesection therapy or in diagnosing advanced disease. It provides little help in detecting early disease, iron store depletion, or iron reaccumulation in these patients.

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#### Diagnosis of early haemochromatosis: relative reliability of the serum ferritin, serum iron and transferrin saturation

L. W. POWELL, JUNE W. HALLIDAY, ANNA RUSSO, AND J. COWLISHAW (introduced by SHEILA SHERLOCK) (*Department of Medicine, University of Queensland, Royal Brisbane Hospital, Brisbane, Australia*) The early detection and treatment of idiopathic haemochromatosis (IHC) is important to prevent complications<sup>1</sup>. Tests currently used for screening relatives of patients are cumbersome and unreliable<sup>2</sup>. The serum ferritin concentration (SF) correlates closely with body iron stores in normal subjects and in patients with iron deficiency or transfusional iron overload, but the evidence for its diagnostic role in early IHC is conflicting<sup>2</sup>. We have studied 43 families with IHC in order to assess the relative values, both singly and in combination, of the serum iron, percent saturation of serum transferrin (TF), and SF concentration.

Forty-three probands and 199 first or second degree relatives were examined. SF levels were measured by a solid phase radioimmunoassay<sup>3</sup>. Increased iron stores were confirmed by desferrioxamine—chelatable iron, hepatic iron concentration, and by quantitative phlebotomy. All probands had classical clinical and pathological features of IHC including cirrhosis and gross increase in total body iron. The serum iron was increased in 37 (90%), the TF saturation in 43 (100%), and the SF also in all 43 (range 670 to 4100  $\mu\text{g/l}$ ) normal ranges 10-150 for females, 20-200 for males). Of the 31 relatives with increased iron stores (16%) the serum iron was raised in 23 (76%), the TF saturation in 31 (100%), and the SF in 30 (98%). However, of the relatives with normal iron stores the serum iron was raised in 17 (10%), the TF saturation was increased in 56 (33%), and SF levels were raised in three (1.8%).

We conclude that the combination of serum iron and SF concentrations is a reliable non-invasive screening test for significant iron overload. If either is abnormal, liver biopsy and hepatic iron

concentration should be performed.

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#### Parenteral 1,25-dihydroxycholecalciferol in hepatic osteomalacia

R. G. LONG, Z. VARGHESE, E. MEINHARD, R. K. SKINNER, M. R. WILLS, AND S. SHERLOCK (*Royal Free Hospital, Pond Street, Hampstead, London*) The aim of this study was to assess the use of 1,25-dihydroxycholecalciferol (1,25-DHCC) in four female patients with biliary cirrhosis and hepatic osteomalacia. Osteoid and total bone volume proportion was assessed by a computerised technique and parathyroid hormone (i-PTH) was measured by radioimmunoassay. 1,25-DHCC 15-30 micrograms in arachis oil was given intramuscularly once a month instead of the previous monthly vitamin D2 100,000 IU in ethyl oleate.

Before treatment with 1,25-DHCC all four patients had bone pains and severe osteomalacia without osteoporosis. Three patients also had a proximal myopathy. Plasma calcium, phosphorus, magnesium, and serum 25-hydroxyvitamin D levels were normal. 47-calcium and phosphorus absorption was normal in three of the four patients. No evidence of hyperparathyroidism was found.

Treatment with 1,25-DHCC for one to five months resulted in loss of bone pain in three patients and resolution of myopathy in two patients. Follow up bone biopsy showed a reduction in osteoid tissue: this indicates healing of osteomalacia. Serum and urine biochemistry and absorption tests changed little with treatment.

It appears that 1,25-DHCC has a direct beneficial effect on bone and muscle in hepatic osteomalacia. This response suggests either a failure of vitamin D 1-hydroxylation or that hepatic osteomalacia is vitamin D2 resistant.

#### Induction of remission in hepatocellular carcinoma with adriamycin

P. J. JOHNSON, ROGER WILLIAMS, H. THOMAS, SHEILA SHERLOCK, AND I. M. MURRAY-LYON (*Liver Unit, King's College Hospital and Medical School, London*,

Royal Free Hospital, London, and Charing Cross Hospital, London) This report concerns the use of adriamycin (60 mg/m<sup>2</sup> intravenously at three-weekly intervals to a total dose of 550 mg/m<sup>2</sup>) in 30 patients, all of whom were considered unfit for transplantation because of extrahepatic spread, tumour metastases, or poor general condition. Twenty-four had underlying cirrhosis.

Of 20 patients followed for at least three months, eight have shown an undoubted response. Four of these are alive and well at seven, 10, 14, and 15 months after diagnosis. Repeat angiography in three cases has shown disappearance of previously extensive tumour circulation and another patient has shown partial clearing of lung metastases. Within three weeks of the first injection there was a fall of more than 50% in alpha fetoprotein levels in seven of the 15 alpha fetoprotein positive patients and all of these showed subsequent clinical remission. In contrast, the eight patients in whom values rose died within three months from tumour progression. Failure of alpha fetoprotein levels to fall within three weeks of instituting therapy is thus of predictive value. Side-effects were restricted to mild nausea and reversible alopecia, and the present response rate—and, in particular, the quality of life—are far better than those obtained in a previous controlled trial of multiple cytotoxic therapy and radiotherapy.

#### Protein induced by vitamin K absence (PIVKA) in liver disease: response to IV vitamin K<sub>1</sub> therapy

F. E. PRESTON, C. D. HOLDSWORTH, AND R. G. MALIA (*Departments of Medicine and Haematology, Royal Infirmary, Sheffield*) Oral anticoagulants compete with vitamin K and precursor proteins (PIVKA) are produced instead of the normal factors II, VII, IX, and X<sup>1</sup>. These have not been studied in liver disease. We have measured PIVKA in jaundiced patients and assessed whether it can be used to predict correction of prolonged prothrombin time by vitamin K<sub>1</sub>.

In seven patients with extrahepatic obstructive jaundice mean PIVKA activity, assessed by a modified thrombotest, was high at 3.7 units/ml (normal 0.1). In these patients prolonged prothrombin times corrected 24 hours after 10 mg intravenous vitamin K<sub>1</sub>. In seven jaundiced patients with intrahepatic disease, PIVKA was normal and vitamin K<sub>1</sub> ineffective.

Using specific factor assays and quantitative immunoelectrophoresis with antibodies raised in rabbits to individual clotting factors, vitamin K responsive patients were shown to have low procoagulant activity but normal amounts of immunologically abnormal precursor protein. Vitamin K unresponsive patients had decreased amounts of both procoagulant activity and of immunologically normal precursor protein.

We conclude that in obstructive jaundice an abnormal precursor protein is synthesised. In hepatocellular disease the precursor protein is structurally normal but reduced in amount. The modified thrombotest detects inhibitory activity of PIVKA and can predict response to vitamin K.

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#### CLINICAL SURGICAL

#### Bacterial flora of the stomach in patients requiring gastric operations

D. GATEHOUSE, F. DIMOCK, D. W. BURDON, J. ALEXANDER-WILLIAMS, AND M. R. B. KEIGHLEY (*The General Hospital, Birmingham*) Gastric resections for ulcer and carcinoma are associated with a high incidence of wound infection<sup>1</sup> which is probably due to disseminating gastrointestinal organisms into the incision at operation<sup>2</sup>. We have therefore studied the microflora of the stomach in normal subjects (n = 11), in duodenal ulcer (n = 30), gastric ulcer (n = 12), and gastric carcinoma (n = 28). Viable counts of aerobic and anaerobic organisms have been performed on the gastric secretions obtained both by preoperative endoscopy and preoperative nasogastric aspirations.

There was a close correlation between the bacterial flora of gastric fluid obtained at preoperative endoscopy compared with operative samples. The mean counts of organisms/ml in gastric juice were as follows: normal subjects  $0 \times 10^0$ ; duodenal ulcer  $1 \times 10^1$ ; gastric ulcer  $5 \times 10^2$ ; carcinoma  $1.3 \times 10^8$ . In 53% of patients with gastric carcinoma viable counts were  $> 10^8$ /ml.

The incidence of wound infection in patients undergoing surgery was as follows: duodenal ulcer 15%, gastric ulcer 29%, and gastric carcinoma 54%. In 70%

of patients developing wound sepsis one or more of the organisms isolated from the incision were the same as those previously identified from gastric juice, and, in these cases, the viable counts of the gastric juice were  $> 10^8$  organisms/ml.

These results indicate that patients likely to develop wound sepsis after gastric surgery can be identified by performing viable counts on gastric aspirates collected at preoperative endoscopy.

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#### Aetiology of gastritis occurring after surgery for peptic ulcer

A. M. HOARE, H. M. CHAPEL, AND J. ALEXANDER-WILLIAMS (*The Queen Elizabeth and General Hospitals, Birmingham, and the Department of Experimental Pathology, University of Birmingham*) Gastritis occurs in the majority of patients who have had operations for duodenal ulcer. The aetiology remains obscure, but one current theory is that it is caused by reflux of bile into the stomach<sup>1</sup>.

We have estimated the concentration of bile in gastric aspirates by the enzymatic method of Fausa and Skålhegg<sup>2</sup>. Gastric biopsies were obtained at endoscopy from the same patients, all of whom had previously had surgery for duodenal ulcer. There was no correlation of gastritis with concentration of bile acids in aspirates obtained from the fasting patient (measured in 105 patients), after pentagastrin (measured in 59 patients), or overnight (measured in 18 patients).

The gastritis occurring after surgery is histologically identical with that of pernicious anaemia. To exclude immunological factors as a cause of postoperative gastritis, immunofluorescent examination has been performed on gastric biopsies from 20 patients with gastritis after surgery for duodenal ulcer. They contained predominantly IgA and no IgG, contrary to findings in pernicious anaemia. In some patients with pernicious anaemia there is cell mediated immunity to gastric antigen, as demonstrated by the leucocyte migration test. We have been able to confirm this in patients with pernicious anaemia, but there was no response to gastric antigen in 20 patients with postoperative gastritis.



Bile reflux or immunological factors are unlikely to be the cause of gastritis occurring after gastric surgery.

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#### Combination of proximal gastric vagotomy with a rotational posterior gastropexy

D. M. HANCOCK, M. Y. SANKAR, J. M. OLD, A. A. K. BOSE, F. LOBO, P. TRINDER, AND P. L. PUNNER (*Department of Surgery, General Hospital, Sunderland, Tyne and Wear*) We have reduced oesophageal reflux symptoms and insulin reactivity after proximal gastric vagotomy (PGV only) by combining PGV with a rotational posterior gastropexy (PGV/pexy). Thirty-nine PGV only cases are compared with 42 PGV/pexy over a one to six year follow-up relating postoperative symptoms to the preoperative state. Our preliminary good results with the pexy procedure have been maintained in this larger series. Gastro-oesophageal competence has also been assessed by oesophageal pH testing or aspiration after stimulation with pentagastrin and a glucose meal. The sensitivity of these tests can be reduced by separating the two stimuli.

Reinnervation across nerve gaps should be prevented after PGV/pexy due to separation of cut nerve twigs. Faber's discriminant (8 mmol H<sup>+</sup>/h) was used to define positive insulin tests (>8) in which a 50% chance of recurrent ulceration has been reported. Six out of 25 PGV only tests were Faber positive at one year, as against only one out of 36 PGV/pexy (P < 0.05).

Postoperative dysphagia has been avoided and heartburn and regurgitation reduced after PGV/pexy. The recurrent ulcer rate may also be reduced by this procedure.

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#### Effect of phenformin on provoked dumping in man

W. G. HUMPHREYS, T. G. PARKS, K. D. BUCHANAN, AND A. H. G. LOVE (*Departments of Surgery and Medicine, Queen's University, Belfast N. Ireland*) Dumping remains a complication of gastric operations: in the past patients with persistent symptoms have benefited from treatment with antidiabetic drugs. This study was undertaken in patients with persistent dumping to investigate the effects of the biguanide phenformin on the symptoms, cardiovascular parameters, and gastrointestinal hormone release. A dumping stimulus of 150 ml of 30% glucose was given on separate occasions before and after 100 mg of phenformin.

Phenformin was found to decrease the induced hyperglycaemia (P < 0.05), decrease the tachycardia (P < 0.05), and decrease the duration and magnitude of the fall in diastolic blood pressure (P < 0.05). There was no significant change in the symptom score or in the decrease in blood volume. Hypertonic glucose stimulated gastrin release (P < 0.01); however, plasma gastrin, insulin, and pancreatic GLI (glucagon-like immunoreactivity) release were not affected by pretreatment with phenformin. The most significant finding was the enhanced release of intestinal GLI in response to oral glucose after phenformin.

These results suggest that phenformin in the 'acute' situation produces objective but not subjective improvement in the experimental dumping reaction. Intestinal GLI is stimulated to a greater degree after phenformin, without an appreciable increase in the severity of dumping. Thus, the rôle of GLI in the pathogenesis of dumping remains uncertain.

#### Extrahepatic biliary atresia: results of surgical treatment

E. R. HOWARD, H. PSACHAROPOULOS, AND A. P. MOWAT (*King's College Hospital, London*) Thirty infants with extrahepatic biliary atresia (EHBA) have undergone laparotomy between June 1973 and April 1977. In 11 cases direct anastomosis between small proximal bile ducts and bowel was attempted ('correctable' EHBA). In four cases operated on at 10-14 weeks, stools became acholic and in two of these the serum bilirubin returned to normal. Eight infants died of liver disease by 12 months of age.

In 15 infants hepatic portoenterostomy

was performed for 'non-correctable' EHBA. Postoperatively, the stools became bile pigmented in 10. Five, four of whom were operated on at 10 weeks, and one at 21 weeks, became free from jaundice and survive at the age of 6 to 51 months. Four have had cholangitis and one required oesophageal transection for bleeding varices. In a further five patients operated at eight (two), 11 (two), and 13 weeks, the serum bilirubin fell substantially but cirrhosis and its complications developed by 12 months of age. One has already died. In the remaining five patients operated on at 9, 11, 12, 14, and 18 weeks of age, stools remained acholic. Four died by 11 months of age.

Bile duct to bowel anastomosis in EHBA is rarely successful. Portoenterostomy performed before intrahepatic changes are advanced gives the best chance of long-term survival.

#### Experimental production of white bile in biliary obstruction

S. J. S. KENT\* AND B. T. JACKSON (*St. Thomas' Hospital, London*) Rous and McMaster<sup>1</sup> concluded that white bile formed in biliary obstruction only when the gallbladder was non-functioning. Our experiments disprove this theory and offer an alternative explanation for the formation of white bile.

Biliary obstruction was produced in 54 New Zealand white rabbits; 24 having complete obstruction, 24 partial obstruction, and six intermittent complete obstruction. In half the animals in each group, the gallbladder was excised at the same time as the obstruction was produced.

Nine out of 24 rabbits with complete obstruction formed white bile, while none of the rabbits with partial obstruction formed white bile (P < 0.01). White bile formation was distributed evenly between those rabbits with the gallbladder intact (five with white bile) and those in whom it had been excised (four with white bile) (P > 0.05). Two out of six rabbits with intermittent obstruction also formed white bile.

It has been shown that the rabbit gallbladder ceases to concentrate bile in biliary obstruction<sup>2</sup> and these findings coincide with the failure of the gallbladder to influence the formation of white bile in the experiments now reported. It is suggested that white bile may form in complete or intermittent biliary obstruction but not in partial biliary obstruction.

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- \*This work was carried out in the preparation of an MS thesis for London University.

## Clinical significance of white bile in obstructive jaundice

S. J. S. KENT\* AND B. T. JACKSON (*St. Thomas' Hospital, London*) Emslie and his colleagues<sup>1</sup>, reporting a small series of nine patients, challenged the unproven surgical aphorism that the presence of white bile in the bile ducts of patients with obstructive jaundice is a sign of liver failure and poor prognosis. This paper reports the results of a study of 69 patients with obstructive jaundice who had white bile and 68 patients (also with obstructive jaundice and of similar age, sex, duration of jaundice, and pre-operative serum bilirubin) who did not have white bile.

After operative relief of jaundice, the rate of decrease in serum bilirubin in patients with white bile, mean  $10.3 \pm 1.37 \mu\text{mol/l/day}$  was not significantly less than the rate in patients who did not have white bile, mean  $15.4 \pm 2.74 \mu\text{mol/l/day}$  ( $P > 0.05$ ). There was also no difference in length of survival after relief of jaundice (allowing for the better prognosis of patients with benign biliary disease). White bile does not appear to indicate either liver failure or poor prognosis.

Malignant disease was the cause of biliary obstruction in 61 of 69 patients with white bile but was present in only 39 of the 68 patients who did not have white bile ( $P > 0.01$ ). This finding might be expected, as the results of experimental work with rabbits<sup>2</sup> have suggested that white bile forms in complete rather than partial biliary obstruction.

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## Accuracy of operative choledochoscopy

A. KAPPAS, J. ALEXANDER-WILLIAMS, R. M.

BADDELEY, N. J. DORRICOOT, M. R. B. KEIGHLEY, G. D. OATES, AND G. T. WATTS (*The General Hospital, Birmingham*) On table cholangiography (OTC) and completion cholangiography have reduced the incidence of retained stones after biliary surgery<sup>1</sup> but both techniques are subject to errors of interpretation and technical failures<sup>2</sup>. Choledochoscopy is an alternative diagnostic technique applicable before and after duct exploration.<sup>3</sup>

We have analysed the experience of all the general surgeons in our hospital in 101 explorations with the rigid choledochoscope in 90 patients. Forty-two choledochoscopies were performed before conventional duct exploration and 59 after.

The findings at pre-exploratory choledochoscopy were correct in 39 examinations with three false negative results. Post-exploratory choledochoscopy correctly identified clear ducts in 51 examinations but stones or debris were missed in eight. The overall accuracy of OTC and completion cholangiography in the same patients was 85% and 78% respectively. There were three false negative (stones) and five false positive (air bubbles). When x-ray was combined with choledochoscopy the diagnostic accuracy was improved, 97% before duct exploration and 90% after.

These preliminary findings suggest that choledochoscopy is not a substitute for OTC but a valuable adjunct. The addition of choledochoscopy should reduce the incidence of retained common bile duct stones, prevent fruitless search for OTC air bubbles, and, possibly make obsolete completion cholangiography.

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## Endoscopic retrograde cholangiography (ERC) in (Oriental) recurrent pyogenic cholangitis (RPC)

SHIU-KUM LAM, KAI-PING WONG, P. K. W. CHAN, H. NGAN, AND G. B. ONG (*Departments of Medicine and Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong and Institute of Radiology, Queen Mary Hospital, Hong Kong*) RPC is characterised by recurrent attacks of

fever, chills and rigors, abdominal pain, and jaundice and in which the extrahepatic and intrahepatic ducts are frequently dilated and contain pigment stones<sup>1</sup>. It is one of the most common causes of acute abdominal emergencies admitted to hospitals in Hong Kong<sup>1</sup>. Information of radiological changes of the biliary system has hitherto been obtained from operative and T-tube cholangiograms, which does not represent the whole spectrum of the disease, as such cholangiograms are performed on patients who require surgery. With the advent of ERC, study of the biliary system can be extended to patients who respond to medical treatment and in whom surgery is not planned. Endoscopic retrograde cholangiograms were studied in 52 patients with RPC. The earlier changes of RPC were identified and found to be confined to the intrahepatic biliary tree. The left hepatic duct was more severely affected than the right hepatic duct and had a higher infestation by clonorchis. The severity of radiological changes correlated well with the duration of illness and the need for surgery. Gall stones were present in 34.2% of the patients and pancreatic ductal abnormality in 7.7%. The decision for surgery could be made early and accurately, and the type of surgery and the assignment of surgeons could be planned in advance—situations which conventional intravenous cholangiograms could not achieve. Cholangitis complicated ERC in 23.1% of the initial 26 patients without antibiotic cover but none of the subsequent 26 in whom this was employed.

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## Single centre double-blind trial of trasyolol therapy in primary acute pancreatitis

C. W. IMRIE, I. S. BENJAMIN, J. C. FERGUSON, W. O. THOMSON, A. J. MCKAY, J. O'NEIL, AND L. H. BLUMGART (*University Department of Surgery, Royal Infirmary, Glasgow*) One-hundred-and-sixty-one consecutive patients with primary acute pancreatitis were admitted to a double blind trial of trasyolol therapy as a supplement to a standard conservative management regimen<sup>1</sup>. The patients were subdivided into group 1 (those less than 60 years old) and group 2 (age 60 years and over) and within those groups were randomly allocated on a double blind basis to either trasyolol therapy in a starter dose of 500,000 KI units and thereafter 200,000

q.i.d. for five days, or to a placebo.

There was an overall mortality rate of 8.7% with seven deaths in both the trasylol and non-trasylol group. In addition to there being no significant difference either overall or within either age group, in respect of mortality there was also no significant difference in the incidence of the major clinical complications of acute respiratory or renal failure, or the development of pancreatic pseudocyst or abscess. Similarly, factors considered of prognostic importance such as severe arterial hypoxaemia ( $\text{PaO}_2 < 60$  mmHg), hypoalbuminaemia ( $< 30$  g/l), hypocalcaemia (serum calcium  $< 1.90$  mmol/l leucocytosis ( $> 15,000/\text{mm}^3$ ) were equally distributed among the patients receiving trasylol and those receiving placebo. This study has shown no benefit in supplementary trasylol therapy in the treatment of primary acute pancreatitis.

#### Reference

<sup>1</sup>Imrie, C. W., and Whyte, A. S. (1975). A prospective study of acute pancreatitis. *British Journal of Surgery*, 62, 490-494.

#### Value of diagnostic peritoneal lavage to determine the severity of acute pancreatitis

M. J. MCMAHON, R. L. BLACKETT, AND I. PICKFORD (University Department of Surgery, The General Infirmary at Leeds) Effective treatment of acute pancreatitis depends upon early recognition of severe attacks, although this can be notoriously difficult.

Diagnostic peritoneal lavage using 1 litre of normal saline was carried out in 27 patients with acute pancreatitis as soon as possible after admission, in order to confirm the diagnosis and establish the severity of the attack. Patients were treated according to a standardised regime. A severe attack was defined as one requiring 14 days hospitalisation, leading to a recognised complication or causing death; there were 10 severe attacks.

There were no complications of lavage. Free peritoneal fluid ( $> 10$  ml) was recovered from nine of the severe patients but only two of the mild ones. The returned lavage fluid was dark straw or brown in colour in nine of the severe patients but in none of the mild ones.

Concentrations of albumin, protein, and transaminase in the return fluid provided a high degree of discrimination between the two grades of severity. There were also differences between the two groups with respect to amylase ( $P < 0.001$ ),

urea ( $P < 0.01$ ), calcium ( $P < 0.01$ ), potassium ( $P < 0.01$ ), bilirubin ( $P < 0.01$ ), white cell count ( $P < 0.02$ ) and alkaline phosphatase ( $P < 0.05$ ).

In five patients lavage correctly predicted a severe attack at a time when it was thought to be mild on clinical grounds.

#### Ileostomy function at home

N. I. MCNEIL, S. A. BINGHAM, A. M. GRANT, AND J. H. CUMMINGS (MRC Dunn Nutrition Unit and Addenbrooke's Hospital, Cambridge) Having an ileostomy is now considered to be compatible with good health. However, most studies of ileostomists have been carried out in hospital and little is known about the ileostomist at home. After a recruitment campaign through the local branch of the Ileostomy Association, 36 ileostomists completed a 24 h urine and ileostomy collection together with nutritional assessment.

Daily ileostomy output was  $760 \text{ g} \pm 322$  SD with Na  $114 \text{ mmol/kg}$ , K  $8.7 \text{ mmol/kg}$ ,  $62 \text{ g}$  solids,  $5.5 \text{ g}$  fat,  $6.2 \text{ g}$  free sugars, and  $0.9 \text{ g}$  starch. Ten subjects with Crohn's disease had a significantly higher ileostomy output,  $1084 \text{ g} \pm 340/\text{day}$ , than the 26 with ulcerative colitis,  $635 \text{ g} \pm 215$ , with correspondingly greater excretions of electrolytes, fat, sugars, and starch. Nine subjects had a raised aldosterone value in either urine or blood.

Almost all subjects had normal haemoglobin, serum iron,  $\text{B}_{12}$ , folate, cholesterol, liver function tests, and plasma Vitamin C. Height, weight, and skinfold thickness as indices of adequate nutrition were within or exceeded published ranges for normal people; all subjects had gained weight since operation.

It is concluded that ileostomists maintain good nutrition after their operation. However, they lose larger quantities of salt and water than suggested by studies of hospitalised patients, and are therefore at continuing risk of electrolyte imbalance, particularly those with Crohn's disease.

#### Is there small intestinal 'adaptation' after colectomy? A study of transport activity in biopsies of ileostomy mucosa

P. C. HAWKER, A. I. MORRIS, AND L. A. TURNBERG (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) It has been suggested that after colectomy the small intestine 'adapts' by enhancing salt absorption and this may be reflected in a

high potential difference (PD) across ileostomy mucosa *in vivo*<sup>1</sup>.

We therefore examined the electrical characteristics and electrolyte transport activity of ileostomy mucosal biopsies searching for evidence of such 'adaptation'. Two suction biopsies of ileostomy mucosa were taken from each of eight patients (*in vivo* PD  $10.78 \pm 2.8$  mV) and these were mounted in specially designed miniature flux chambers and bathed in oxygenated buffer at  $37^\circ$ .

Compared with values from our laboratory for normal ileum obtained at operation, the PD was higher ( $5.14 \pm 0.5$  mV against  $3.3 \pm 0.3$  mV) as was tissue resistance ( $73.1 \pm 8.9 \Omega \text{ Cm}^{-2}$  against  $40.3 \pm 2.8 \Omega \text{ Cm}^{-2}$ ) but the short-circuit current was lower ( $44.5 \pm 6.6 \mu\text{A.Cm}^{-2}$  against  $94 \pm 7 \mu\text{A.Cm}^{-2}$ ).

Isotopic flux measurements demonstrated a net sodium absorption ( $2.42 \pm 1.13 \mu\text{Eq.Cm}^{-2}.\text{h}^{-1}$ ,  $n = 4$ ) rising on addition of  $10 \text{ mM}$  glucose ( $8.96 \pm 3.2 \mu\text{Eq.Cm}^{-2}.\text{h}^{-1}$ ) both values being similar to 'normal' ileum.

In three of four tissue pairs no net chloride transport was demonstrated, the fourth from a patient with ileostomy diarrhoea showed a large chloride secretion.

We conclude that the high *in vivo* ileostomy PD simply reflects a local increase in mucosal resistance and is not due to enhanced sodium absorption. We have not demonstrated evidence of ileal 'adaptation'.

#### Reference

<sup>1</sup>Isaacs, P. E. T., Horth, C. E., and Turnberg, L. A. (1976). The electrical potential difference across human ileostomy mucosa. *Gastroenterology*, 70, 52-58.

#### Colonic motility and clinical results after multiple transverse taeniamyotomy for diverticular disease

M. PESCATORI (Institute of Clinical Surgery, Catholic University, Rome, Italy) The purpose of our investigation was to evaluate the effect of multiple transverse taeniamyotomy (TTM) on sigmoid motility and clinical picture of eight patients affected by symptomatic uncomplicated diverticular disease of the sigmoid, selected for the operation after the failure of antispasmodics, high residue diet, and bran as medical therapy<sup>1</sup>.

We recorded sigmoid intraluminal pressures and the manometric tracings were correlated with the corresponding photo-fluorograms before and after the operation for a period of one year. Motor activity



was recorded at 25, 20, and 15 cm from anal verge by open-ended perfused catheters under basal condition, after a standard meal and after prostigmine (B, M, P). Motility indices were computed and the results shown in a Table.

A significant (*t* test) decrease under stimulus was found in patients who underwent TTM.

These functional changes were accompanied by a marked clinical recovery, expressed in terms of lower abdominal pain and of weekly bowel movements (WBM).

Considering functional and clinical disadvantages reported after colectomy and longitudinal myotomy (Reilly's operation)<sup>1,2,3</sup> and observing our results after TTM, even though they are short-term results, we conclude that the later operation is a simple, low risk, rational, and effective procedure for the treatment of diverticular disease with muscular hypertrophy and high intracolonic pressure, not responding to medical and dietetic regimen.

#### References

- <sup>1</sup>Hodgson, J. (1973). Transverse taeniamyotomy for diverticular disease. *Diseases of the Colon and Rectum*, 16, 4, 283-289.
- <sup>2</sup>Parks, T. G. (1970). Rectal and colonic studies after resection of the sigmoid for diverticular disease. *Gut*, 11, 121.
- <sup>3</sup>McGinn, F. P. (1976). Distal colomyotomy: follow-up of 37 cases. *British Journal of Surgery*, 63, 309-312.

#### Factors influencing survival of patients with colorectal cancer in a regional hospital

P. G. GILL, P. J. MORRIS, AND M. G. KETTLEWELL (*Nuffield Department of Surgery, University of Oxford, Radcliffe Infirmary, Oxford*) The survival of patients with colorectal cancer treated outside specialised centres is thought to be poor<sup>1</sup>. We examined the records of 335 patients who were treated at one regional hospital between 1966 and 1971. Actuarial survival curves were obtained and the influence of clinical and pathological factors on survival were analysed using the log-rank test<sup>2</sup>.

One-hundred-and-ninety-two patients had resection for cure with an adjusted five-year survival of 53.8%, while 37.2% of patients survived overall.

Pathological stage was the most important determinant of prognosis, but a significantly worse survival was associated with emergency presentations, age less than 35 years, and with staged operative

procedures. Significantly better results were achieved in the cases of upper rectal growths than in cases affecting the colon or lower rectum. The occurrence of post-operative sepsis had no effect on survival.

Suture-line and wound recurrence rates were high, suggesting that technical factors influenced the results. However, the small proportion of A and B lesions in the series indicates that delay in presentation and diagnosis is also involved.

#### References

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- <sup>2</sup>Peto, R., *et al.* (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II Analysis and examples. *British Journal of Cancer*, 35, 1-39.

#### Results of local excision for 'early' colorectal cancer

M. R. LOCK, JEAN K. RITCHIE, AND H. E. LOCKHART-MUMMERY (*St. Mark's Hospital, London*) A retrospective analysis is presented of 140 patients with an 'early' single adenocarcinoma of the colon or rectum treated at St. Mark's Hospital by local excision between 1 January 1948 and 31 December 1972 and followed up until 31 July 1976. Patients with ulcerative colitis or adenomatous polyposis coli were excluded.

None of the 30 patients with pedunculated colonic tumours developed a recurrence.

Eight-eight patients with pedunculated rectal tumours were treated; 68 required no further operation, although one died with widespread metastases. Twenty patients underwent further operation; 16 for suspected residual tumour and four later for recurrent disease.

Only 22 patients with non-pedunculated rectal tumours were treated. These tumours were excised by peranal or trans-sphincteric approaches utilising various techniques. Five patients underwent early reoperation for suspected incomplete excision, although residual tumour was found only in two. Two other patients developed a recurrence.

Although 15% of all colorectal cancers resected at this hospital are Dukes A cases, only about 4% were treated by local excision during these 25 years. Perhaps local excision should be considered more frequently. Close consultation between clinician and pathologist is essential as poorly-differentiated or incompletely excised tumours need early major surgery.

#### Clinical trial of cytotoxic perfusion for colorectal liver metastases

I. TAYLOR (*Department of Surgery, Liverpool*) (introduced by Professor R. SHIELDS) Multiple liver metastases are frequently found at laparotomy for colorectal cancer, often as an unexpected finding<sup>1</sup>. In these cases the primary lesion, if resectable, should probably be removed but whether any specific treatment should be prescribed for the liver metastases is not clear.

A clinical trial to assess the value of different perfusion techniques in the management of colorectal liver metastases is presented. The perfusion with 5-fluorouracil was commenced at the time of resection of the primary tumour when palpable liver metastases were found. In terms of survival no benefit was found with hepatic artery ligation and perfusion (mean 3.0 ± 2.0 months) and with portal vein perfusion alone (mean 4.1 ± 3.8 months) compared with the control group. However, the combination of the two improved the survival rate (mean 9.8 ± 3.4 months) and had palliative value.

It would appear that little is gained by treating colorectal liver secondaries at the time of initial surgery by either hepatic artery ligation and perfusion or by portal vein perfusion alone. However, the combination may confer some benefit in prolonging symptom-free survival.

#### Reference

- <sup>1</sup>Oxley, E. M., and Ellis, H. (1969). Prognosis of carcinoma of the large bowel in the presence of liver metastases. *British Journal of Surgery*, 56, 149-152.

#### Perfusion of the rat small intestine

H. J. LEESE, J. R. BRONK, P. A. INGHAM, AND J. PRENDERGAST (introduced by G. WATKINSON) (*Department of Biology, University of York, York*) Two preparations for the perfusion of the rat jejunum will be presented. In the first, a stream of oxygenated Krebs Ringer bicarbonate medium at 37°C is recirculated through the lumen of an isolated loop, by gas-lift. The serosal surface is bathed in a similar solution. The preparation to be demonstrated incorporates an on-line Auto-analyser system for the continuous monitoring of glucose, or lactate in the perfusion media. A major disadvantage with this type of preparation is that absorbed solutes are not readily cleared from the basal surfaces of the epithelial

cells as they would be *in vivo* but have to traverse the submucosa, and cut mesenteric and lymph vessels.

This disadvantage is overcome in the second preparation in which the blood vessels serving the jejunum are cannulated and the vascular bed is perfused, in addition to the lumen<sup>1</sup>. The medium for vascular perfusion includes washed human erythrocytes and serum albumin. The preparation is stable for at least 40 minutes during which time it is possible to monitor the vascular appearance of sugars or amino acids added to the luminal fluid.

#### Reference

- <sup>1</sup>Hanson and Parsons. (1976). *Journal of Physiology*, 255, 77.

#### PLENARY SESSION

### Parotid gland function in patients with pancreatic disease

K. E. L. MCCOLL, M. J. BRODIE, R. WHITESMITH, AND T. J. THOMSON (*Department of Gastroenterology, Stobhill Hospital, Glasgow*) A close functional relationship exists between the exocrine pancreas and the parotid glands<sup>1,2</sup>. We report our results of parotid gland function in patients with pancreatic disease.

Parotid salivary gland function was assessed in 12 patients with pancreatic exocrine insufficiency due to chronic pancreatitis and in 12 control subjects matched for age, sex, and alcohol consumption. Pure parotid juice was collected for five minutes during lingual stimulation using 10 ml 10% citric acid. The volume of juice produced and its concentration of amylase and various electrolytes were measured. The concentrations of sodium and bicarbonate were significantly reduced in the patients with chronic pancreatitis ( $31 \pm 20$  and  $26 \pm 13$  mmol/l) compared with the controls ( $70 \pm 9$  and  $46 \pm 9$  mmol/l) ( $P < 0.001$ ).

Parotid and pancreatic function was simultaneously assessed by measuring their excretion of injected <sup>75</sup>-selenomethionine after a Lundh test meal in eight patients with chronic pancreatitis, eight with pancreatic carcinoma, and 12 control subjects. In the patients with chronic pancreatitis both the pancreatic and parotid excretion was impaired to a similar extent. In the patients with pancreatic carcinoma there was only minimal impairment of parotid excretion with marked impairment of pancreatic excretion.

The mean pancreatic/parotid ratio for excretion of <sup>75</sup>-selenomethionine was 2.8 (range 1.7-4.8) in chronic pancreatitis and 0.8 (range 0.2-1.6) in pancreatic carcinoma.

This combined pancreatic/parotid function test may help to differentiate chronic pancreatitis from pancreatic carcinoma.

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<sup>2</sup>Pinheiro, C. E., Tarzia, O., and Taga, E. M. (1972). The influence of endocrine and exocrine pancreas on the carbonic anhydrase activity of the rat salivary glands. *Revista Brasileira de Pesquisas Médica Biologia*, 5, 1-5.

### Separation and characterisation of the organelles in peroral jejunal biopsies from the dog

R. M. BATT, B. M. BUSH, AND T. J. PETERS (*Department of Medicine, Royal Postgraduate Medical School and Royal Veterinary College, London*) Naturally occurring malabsorptive syndromes have been described in the dog including degenerative atrophy of the pancreas and various small intestinal disorders<sup>1</sup>, some of which resemble coeliac disease. In order to examine the small intestine in these cases a technique has been developed for peroral jejunal biopsy. This has been used in conjunction with an analytical subcellular fractionation procedure and enzymic analysis to characterise the various organelles in normal and diseased mucosa.

A Watson paediatric capsule was passed to the stomach with an outer flexible sheath protecting the tubing. The sedated dog was then placed in right lateral recumbency and the capsule positioned at the pylorus with fluoroscopic screening. Using a guide wire and assisted by peristalsis, the capsule was passed into the duodenum and on to the proximal jejunum.

The biopsies were fractionated by isopycnic centrifugation on a continuous sucrose density gradient<sup>2</sup>. In control tissue the following organelles were characterised, with marker enzymes and modal densities between parentheses: peroxisomes (catalase, 1.21); brush borders (alkaline phosphatase, leucyl-2-naphthylamidase, Zn-resistant  $\alpha$ -glucosidase,  $\gamma$ -glutamyl transferase, 1.19); lysosomes (N-acetyl- $\beta$ -glucosaminidase,  $\alpha$ -mannosidase, acid phosphatase, 1.19); mito-

chondria (malate dehydrogenase, 1.18); endoplasmic reticulum (Tris-resistant  $\alpha$ -glucosidase, 1.16); basal-lateral membranes (5'-nucleotidase, 1.12); cytosol (lactate dehydrogenase). Homogenisation in digitonin (0.2 mg/ml) resulted in a clear separation of brush borders and lysosomes.

Jejunal mucosa can now be simply obtained from the dog and a complete resolution of all the organelles of the enterocyte achieved. Application of these techniques will include a study of the comparative aspects of small intestinal diseases and investigations of the physiology and biochemistry of enterocyte function.

#### References

- <sup>1</sup>Hill, F. W. G. (1972). *Journal of Small Animal Practice*, 13, 575-594.  
<sup>2</sup>Peters, T. J. (1976). *Clinical Science and Molecular Medicine*, 51, 557-574.

### Subcellular distribution of di-, tri-, tetra- and penta-peptidase in human jejunum

J. A. NICHOLSON AND T. J. PETERS (*Department of Medicine, Royal Postgraduate Medical School, London*) Dipeptide hydrolase activity has been recently shown to be almost entirely located in the cytosol of the enterocyte<sup>1</sup>. As larger peptides are also found in the intestinal lumen after a protein meal<sup>2</sup>, the subcellular distribution of hydrolases acting upon peptides of two to five amino acid residues has been investigated.

Jejunal biopsies from control subjects were homogenised and subjected to sucrose density gradient centrifugation<sup>3</sup>. The distributions of mitochondrial, endoplasmic reticulum, lysosomal, peroxisomal, brush border, basal-lateral membranes and cytosolic marker enzymes were determined and compared with those of the peptidases.

Peptidase activities, assayed at pH 8.0-8.5, were found in the cytosol and in the brush border fraction but in no other organelle. There were striking differences in the distribution of peptidase between the two fractions depending on the chain-length of the substrate. Almost all activity (96-98%) against dipeptides was found in the cytosol. However, for tri-leu and tri-phe, hydrolase activity was divided nearly equally between the two fractions. Rather less tri-gly hydrolase activity (20%) was associated with the brush border. For tetra-phe and tetra-gly most of the peptidase was in the brush border (73% and 88% respectively). Penta-gly hydrolase

sis was exclusively localised to the brush border but approximately 50% of the activity against penta-phe was found in the cytosol.

These data are in agreement with concepts of peptide transport which suggest brush border hydrolysis of tetra and longer peptides and intracellular hydrolysis of dipeptides and triglycine.

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<sup>2</sup>Matthews, D. M., and Adibi, S. A. (1976). *Gastroenterology*, 71, 151-161.  
<sup>3</sup>Peters, T. J. (1976). *Clinical Science and Molecular Medicine*, 51, 557-574.

#### Isolation and characterisation of polypeptide hormone storage granules from human jejunum

M. G. BRYANT, S. R. BLOOM, P. E. JONES, AND T. J. PETERS (*Department of Medicine, Royal Postgraduate Medical School, London*) It is now apparent that abnormalities of gut hormone release are an important aspect of human intestinal disease. Little work has been undertaken on the synthesis, storage and release mechanisms for these hormones. Analytical subcellular fractionation<sup>1</sup> of jejunal biopsy specimens in conjunction with specific radioimmunoassays have been used to isolate and characterise the hormone-containing granules from normal human jejunum.

Crosby capsule specimens of jejunum were homogenised in 0.3 M sucrose containing 1 mM Na<sub>2</sub> EDTA and 20 mM ethanol and after low speed centrifugation the 8000 g-min post-nuclear supernatants were fractionated by sucrose density gradient centrifugation. Aliquots of the gradient fractions were assayed for organelle marker enzymes and immunoreactive hormone content. Gastrin and GIP showed similar distributions with distinct particulate components at a modal density (MD) of 1.22. Granules containing VIP (MD = 1.17), motilin (MD = 1.20), and secretin (MD = 1.24) were clearly separated. VIP immunoreactivity was also found in the low speed pellet probably reflecting its partial localisation to neuronal elements.

These experiments demonstrate the presence of at least four distinct populations of gut hormone-containing granules in human jejunum. This combination of techniques will make it possible to study the dynamic changes in granule density

under physiological conditions and to detect alterations in intestinal disease.

#### Reference

- <sup>1</sup>Peters, T. J. (1976). *Clinical Science and Molecular Medicine*, 51, 557-574.

#### In vitro uptake of iron by human duodenal biopsies

T. M. COX AND T. J. PETERS (*Department of Medicine, Royal Postgraduate Medical School, London*) The duodenal enterocyte is the primary regulatory site for iron absorption. The absorption process involves several steps including uptake by the brush border, transfer to intracellular binding proteins and organelles, and transport across the basal-lateral cell membranes to the portal plasma. The controlling steps and, in particular, the process whereby iron deficiency leads to enhanced iron absorption, are unknown. In order to investigate these mechanisms in man a technique has been developed to study *in vitro* the uptake and intracellular processing of iron compounds by human duodenal mucosa.

Portions of mucosal biopsies were incubated in oxygenated buffered balanced salt solution containing <sup>57</sup>Co-labelled cyanocobalamin as a non-absorbed marker for extracellular fluid. Iron complexes [<sup>59</sup>Fe<sup>3+</sup>] were prepared with a molar excess of nitrilotriacetate acid and were added to the medium to final concentrations of 18-450 μM. After incubation at 37°C the tissue was removed, rinsed, blotted, weighed and the uptake of <sup>59</sup>Fe determined.

Iron uptake was linear in the above concentration range for up to 20 minutes; the extracellular fluid marker equilibrated within five minutes. Uptake of 18 μM Fe<sup>3+</sup> was inhibited by 48% when 0.1 mM dinitrophenol and 10 mM sodium fluoride were added to the medium. Uptake of iron over the range 17°-37° was shown to be highly dependent on the temperature (Q<sub>10</sub> = 2.8) indicating that iron uptake by the human duodenum is at least partially an energy requiring process. Studies on duodenal biopsies from patients with iron deficiency demonstrated a striking increase in the rate of iron uptake indicating that at least part of the controlling process for iron absorption is at the entry step.

#### Role of mitochondria in iron transport by guinea-pig small intestine

J. HOPKINS, T. M. COX, AND T. J. PETERS

(*Department of Medicine, Royal Postgraduate Medical School, London*) It has been suggested that the mitochondria of the enterocyte play a role in the regulation of intestinal iron absorption<sup>1</sup>. The subcellular distribution of labelled and of total iron has been determined with analytical centrifugation techniques in guinea-pig enterocytes during the absorption of <sup>59</sup>ferric chloride.

An injection of 90 nmol <sup>59</sup>FeCl<sub>3</sub> in 0.15 M NaCl—5 mM HCl was made into 15 cm closed jejunal loops of anaesthetised guinea-pigs. After periods from 10 to 180 minutes the contents of the loops were removed and the enterocytes isolated. The enterocytes were homogenised and the subcellular organelles separated by either isopycnic or rate zonal centrifugation on sucrose density gradients<sup>2</sup>. There was rapid binding of labelled iron to the brush borders and uptake into the soluble fraction of the cell. Approximately 30% of the radioactivity was localised to the mitochondria. Addition of <sup>59</sup>FeCl<sub>3</sub> directly to the enterocyte homogenate was not associated with uptake of the label by mitochondria. Subfractionation of the mitochondria by either sonication or digitonin treatment showed that most of the iron was associated with the mitochondrial matrix or inner membranes indicating active uptake of the metal ion by this organelle<sup>3</sup>. Chromatographic analysis<sup>4</sup> of the mitochondrial fractions showed that the labelled iron was mainly (85%) associated with a transferrin fraction with little binding to ferritin, haemprotein or haemosiderin fractions. These experiments demonstrate that iron is rapidly localised to the interior of intestinal mitochondria during its absorption supporting the proposed role of this organelle in the regulation of iron absorption.

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<sup>2</sup>Peters, T. J., and Shio, H. (1976). *Clinical Science and Molecular Medicine*, 50, 355-366.  
<sup>3</sup>Romslo, I., and Flatmark, T. (1974). *Biochimica Biophysica Acta*, 347, 160-167.  
<sup>4</sup>Drysdale, J. W., and Ramsay, W. N. M. (1965). *Biochemical Journal*, 95, 282-287.

#### Immunity and the hyposplenism of coeliac disease (CD)

A. W. BULLEN, R. HALL, E. M. COOKE, AND M. S. LOSOWSKY (*Department of Medicine, University of Leeds, St. James's Hospital, Leeds*) Evidence for the immunological



importance of splenic atrophy in CD is confined to the demonstration of the association between hyposplenism and impaired antibody production to an experimentally administered coliphage antigen<sup>1</sup>. We have assessed humoral and cell mediated immunity to naturally occurring, frequently encountered antigens in normal subjects and treated coeliac patients with hyposplenism or normal splenic function.

Splenic function was assessed by Tc<sup>99m</sup> labelled heat damaged red cell clearance in 28 patients; 13 showed hyposplenism. Serum antibodies to 11 types of *E. coli* were measured<sup>2</sup> and recall skin tests with PPD, candida, and streptokinase-streptodornase were performed.

In coeliac patients with normal splenic function, the number of *E. coli* antibodies was significantly higher than in 42 healthy controls ( $P < 0.05$ ). In coeliacs with hyposplenism the number ( $P < 0.02$ ) and maximum titre ( $P < 0.05$ ) of *E. coli* antibodies was significantly lower than in those with normal splenic function.

Both groups of coeliacs had significantly fewer positive skin tests than controls; there was no significant difference between the two groups.

The results suggest that humoral immunity is impaired in patients with CD and hyposplenism. The increase in *E. coli* antibodies in coeliacs with normal splenic function may reflect the impaired mucosal resistance in CD. The general decrease in skin reactivity may reflect impaired cell mediated immunity during antigen exposure, but seems unrelated to hyposplenism.

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- <sup>2</sup>Webster, A. D. B., Efler, T., and Asherson, G. L. (1974). *Escherichia coli* antibody: a screening test for immunodeficiency. *British Medical Journal*, 2, 16-18.

#### Mechanisms of thrombocytosis in coeliac disease (CD)

A. W. BULLEN, R. HALL, R. C. BROWN, AND M. S. LOSOWSKY (Department of Medicine, University of Leeds, St. James's Hospital, Leeds) Thrombocytosis is well documented in untreated CD and is usually attributed to a non-specific reaction to the bowel lesion, or to iron deficiency<sup>1</sup>. However, hyposplenism may also cause

thrombocytosis, and hyposplenism also occurs in CD<sup>2</sup>. We have compared platelet counts in treated and untreated CD and measured splenic function to assess the relationship between the bowel lesion, hyposplenism, and thrombocytosis.

Platelet counts were significantly higher in 26 untreated coeliacs than in 32 treated coeliacs ( $P < 0.001$ ). Ten of 26 untreated patients (38%) and four of 32 treated patients (13%) had platelet counts greater than 350 000/mm<sup>3</sup> (range 360 000-780 000). 10 of these 14 patients had blood film evidence of hyposplenism on careful study.

Splenic function was assessed by Tc<sup>99m</sup> labelled heat damaged red cell clearance in 30 patients. In untreated CD, platelet counts were significantly higher ( $P < 0.05$ ) in nine hyposplenic patients than in 10 patients with normal splenic function; counts fell after treatment in 16 out of the 19 patients. In treated patients the platelet count correlated with heat damaged red cell clearance times ( $P < 0.01$ ). No correlation with serum iron, B<sub>12</sub> or folate levels was found.

These results suggest that both hyposplenism and activity of the bowel lesion contribute to the thrombocytosis of CD and that the platelet count may be a guide to splenic function.

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- <sup>2</sup>McCarthy, C. F., Fraser, I. D., Evans, K. T., and Read, A. E. (1966). Lymphoreticular dysfunction in idiopathic steatorrhoea. *Gut*, 7, 140-148.

#### Dual isotope method of clinical measurement of fat absorption using tritiated glycerol triether—results in 101 subjects

J. F. MACKENZIE, L. M. NELSON, E. ROBERTSON, AND R. I. RUSSELL (Gastroenterology Unit, Royal Infirmary, Glasgow) Tritiated glycerol triether has been validated as a non-absorbable oil-phase marker in man<sup>1</sup>. Oral administration of <sup>14</sup>C labelled triolein, a typical dietary triglyceride, together with the <sup>3</sup>H labelled marker enables the percentage absorption of triolein to be calculated from the ratio of the isotopes in an aliquot of faeces.

This technique has been applied clinically in 101 subjects to assess its role in the diagnosis of fat malabsorption. Twenty-five normal subjects had greater than 95% absorption (range 96.4-100%) and a faecal fat excretion of less than 21

mmol/24 h. Seventy-six patients with diarrhoea, known GI disease, or suspected steatorrhoea underwent the test concurrently with routine three day gravimetric faecal fat estimation. These patients were divided into three groups on the results of the tests: (1) 26 patients had abnormal absorption (less than 95%, range 0.01-93.7%) and faecal fat excretion greater than 21 mmol/24 h (range 26-556); this group included one patient with pancreatectomy (0.01% absorption), five with pancreatic insufficiency, 11 coeliacs, and four with Crohn's disease; (2) 26 patients had no abnormality of fat absorption or faecal fat excretion; (3) 20 patients were found to have steatorrhoea (range 22-164 mmol/24 h) but normal absorption. Ten of these patients had blind loop syndrome or jejunal overgrowth and five had coeliac disease.

This test is of value in the investigation of fat malabsorption and has distinguished two types of steatorrhoea, one of these due to malabsorption of triglyceride. The excess faecal lipid in the second type may originate from cell-exfoliation, bacteria or sterols of unknown origin.

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#### Third division of the autonomic nervous system. An important element in gut control

A. C. BISHOP, J. M. POLAK, A. M. J. BUCHAN, S. R. BLOOM, AND A. G. E. PEARSE (Department of Histochemistry and Medicine, Royal Postgraduate Medical School, London) The autonomic nervous system was, classically, considered to consist of two divisions, cholinergic and adrenergic. However, in the gut wall, for example, electron microscopy shows three distinct groups of nerve types: (1) the adrenergic nerves, containing small vesicles (300-500 Å); (2) the cholinergic nerves, mainly agranular; (3) nerves with large granules (800-2000 Å).

This third group has been termed purinergic by Burnstock<sup>1</sup>. The increasing number of peptides common to brain and gut has led to discovery of a dual localisation of peptides in both the endocrine cells and peripheral nerves of the gut.

Immunocytochemical light and EM studies carried out on 10 surgical biopsies of human gut and pancreas have localised

vasoactive intestinal peptide (VIP) both in sparse endocrine cells and in numerous intramural nerves.

VIP appears to be present in the nerve fibres and terminals. The granules are large (700-1600 Å) and electron dense and appear to correspond to the 'purinergic' nerves. Other peptides, including substance P, somatostatin, and the newly discovered bombesin, have also shown dual localisation. The granules appear to fall with the 'purinergic' grouping but are distinguishable from each other.

The study of gut hormones and their actions has, thus, led to a new concept of a three-part autonomic control system consisting of adrenergic, cholinergic, and peptidergic nerves. The recognition of this new system may be helpful in the understanding of some puzzling aspects of gut pathology.

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- <sup>1</sup>Burnstock, G. (1972). Purinergic nerves. *Pharmacology Review*, 24, 509.

#### VIP release in intestinal ischaemia

I. M. MODLIN, S. R. BLOOM, AND S. J. MITCHELL (*Departments of Surgery and Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London W12, UK*) Vasoactive intestinal peptide (VIP) has been isolated in large quantities from the gastrointestinal tract of all mammalian species. It has a wide range of potent pharmacological actions including tachycardia and a powerful hypotensive effect. We have therefore investigated its possible role in the haemodynamic sequelae of gut ischaemia.

In six anaesthetised pigs small intestinal ischaemia was produced by isolating the superior mesenteric axis and applying a clamp. Portal, peripheral and arterial cannulae were inserted for plasma sampling. Constant recording of vital signs was performed by an arterial pressure transducer, CVP and ECG monitor. Two fifteen-minute episodes of intestinal ischaemia were produced with a 30-minute rest interval. After the first ischaemic period portal venous VIP rose from a mean basal of  $15 \pm 5$  (SEM) to a mean peak of  $45 \pm 9$  pmol/l. Plasma motilin concentrations remained unchanged and enteroglucagon levels did not change significantly. The arterial blood VIP concentrations reflected the portal levels, though the rise was less marked. Concomitant with the release of VIP a rapid fall in blood pressure from 110/70 to 90/60 mm mercury, and a rise in

pulse rate from 86 to 125/min was seen. After the second ischaemic period portal VIP rose from  $18 \pm 6$  to  $100 \pm 12$  and a greater fall of blood pressure was seen.

Explanation of the profound circulatory changes of gut ischaemia is complex and uncertain. Since VIP is a potent vasodilator which is found throughout the gastrointestinal tract, its apparently specific release by intestinal ischaemia may be a factor in the serious haemodynamic alterations after gut infarction.

#### VIP infusion in man

S. R. BLOOM, S. J. MITCHELL, S. DOMSCHKE, W. DOMSCHKE, P. MITZNEGG, G. LUX, U. STRUNZ, AND L. DEMLING (*Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, and Department of Medicine, University of Erlangen, Nuremberg, Erlangen, Germany*) The physiological role of the powerful new hormonal peptide, VIP, is still undecided. We have therefore tested the effects of exogenous administration in man.

Four healthy male volunteers received separate 30 minute porcine VIP infusions of 4, 8, and 16 pmol/kg/min. Plasma VIP rose from mean basal values of 4 pmol/l to between 20 and 100 pmol/l with the low dose, to  $154 \pm 22$  (SEM) with the medium dose and to  $351 \pm 12$  with the high dose. After discontinuing the infusion plasma VIP fell precipitously with a half-life of 1-22 minutes from the medium dose and 1-03 minutes from the high dose infusion. The calculated metabolic clearance rate was  $53 \pm 8$  ml/kg and  $46 \pm 2$  ml/kg respectively. The medium VIP dose resulted in marked cutaneous flushing which was even more intense with the 16 pmol/kg/min dose. Pulse rate rose by 35 beats per minute and diastolic blood pressure fell 15 mm of mercury with the high dose infusion. There was also a small rise in plasma glucose and calcium concentrations.

Animal experiments suggest that similar amounts of VIP are required to produce the gastric inhibitory and pancreatic stimulatory effects of VIP. As no release of VIP is seen in man after a meal and levels above 20 pmol/l are rarely observed, it seems unlikely, therefore, that VIP would play a significant role as a circulating hormone. Its very rapid half-life is more in favour of the previously suggested role as a local hormone or neurotransmitter substance<sup>1</sup>.

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#### Release of VIP by duodenal acidification in man

S. R. BLOOM, S. J. MITCHELL, G. R. GREENBERG, N. CHRISTOFIDES, W. DOMSCHKE, S. DOMSCHKE, P. MITZNEGG, AND L. DEMLING (*Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London and Department of Medicine, University of Erlangen, Nuremberg, Erlangen, Germany*) Vasoactive intestinal peptide (VIP) is known to be a potent stimulator of pancreatic bicarbonate juice production and is present in high concentration in the duodenal mucosa, greatly exceeding that of secretin. We have, therefore, investigated its release after duodenal acidification.

Ten volunteers were studied during a basal period and after introduction via a duodenal tube of 50 ml 0.1 normal HCl over three minutes. Plasma was assayed for VIP, secretin, and motilin by highly sensitive radioimmunoassays showing no hormonal cross-reaction. Basal VIP was  $0.46 \pm 0.38$  (SEM) pmol/l and rose at four minutes by  $0.8 \pm 0.3$ , at 10 minutes by  $8.0 \pm 1.0$ , and by  $6.1 \pm 1.2$  at 30 minutes. In contrast, the rise of plasma secretin was much more rapid and short lived, basal  $1.7 \pm 0.6$ , four minute increment  $7.4 \pm 1.1$ , 10 minute increment  $0.3 \pm 0.8$ , and 30 minute increment  $0.7 \pm 0.6$ . Motilin showed an intermediate pattern with a basal concentration of  $32 \pm 9$ , four minute increment of  $17 \pm 3$ , 10 minute increment of  $6 \pm 1$ , and a 30 minute increment of  $6 \pm 4$ .

Thus, VIP does not appear to be an important circulating hormone controlling the pancreas, as its potency in man is much less than that of secretin. VIP is a potent stimulant of small intestinal juice production. The rise of circulating VIP may be an 'over-flow' phenomenon and may thus be an indication of the important local role of VIP in the intestinal response to acid.

#### Altered intestinal sensitivity to bile acids and small intestinal secretion in irritable bowel syndrome associated with diarrhoea

J. RASK-MADSEN, E. ODDSSON, AND E. KRAG (*Department of Medicine C, Gastroenterological Division, Herlev Hospital, University of Copenhagen, Denmark*) An

abnormal intestinal motility cannot account for the great loss of fluid observed in irritable bowel syndrome associated with diarrhoea (IBSD). Since the colonic absorptive capacity has proved normal in this condition<sup>1</sup> we found it pertinent to focus on the small intestine. In order to elucidate whether other secretory stimulants than those of the cAMP-system may be involved in the mechanism of diarrhoea in IBSD intestinal secretion was produced by glycochenodeoxycholic acid (GCDC). We studied net movements of water and electrolytes and the bi-directional fluxes of Na, Cl, and K by perfusing 25 cm of the terminal ileum of 10 healthy volunteers and six patients with IBSD. Perfusates were isosmotic saline solutions containing glucose, 22-Na, 42-K, and 36-Cl. Dilution marker was 51-Cr-EDTA. 0.2-5 mM GCDC was added. In normal subjects 1 mM stimulated absorption, while 1.5-2.5 mM decreased absorption and evoked secretion of water and electrolytes. In IBSD secretion occurred spontaneously. GCDC 0.25 mM facilitated the absorptive processes, while 1.0-2.5 mM caused profuse secretion. Changes in plasma to lumen fluxes were responsible for spontaneous secretion in IBSD, while GCDC reduced the opposite fluxes equally in both groups. In conclusion, the ileal epithelium in IBSD shows increased sensitivity to GCDC and seems to be prestimulated by some as yet unidentified agent which is not a stimulant of cAMP and influences the fluxes in the same way as prostaglandin E<sub>1</sub><sup>2</sup>.

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<sup>2</sup>Matuchansky, C., and Bernier, J. J. (1973). Effect of prostaglandin E<sub>1</sub> on glucose, water, and electrolyte absorption in the human jejunum. *Gastroenterology*, 64, 1111-1118.

#### Mother-to-infant transmission of hepatitis B virus

M. J. TARLOW, A. DERSO, E. H. BOXALL, AND T. H. FLEWETT (*Paediatric Teaching Unit and Regional Virus Laboratory, East Birmingham Hospital, Bordesley Green East, Birmingham*) This study was designed to determine the importance of vertical (mother-to-infant) transmission of hepatitis B virus surface antigen (Hb<sub>s</sub>Ag) in the population.

In the West Midlands (birth rate 80 000 a year) 297 symptomless Hb<sub>s</sub>Ag carrier mothers were detected between April 1974 and May 1977 by routine screening at antenatal clinics. Cord blood was received from

192 of the 232 babies so far delivered. Eighty-seven (45.3%) were positive for Hb<sub>s</sub>Ag by radioimmunoassay. The antigen is usually present in very low titre and by six weeks it is present in a smaller proportion of infants at a still lower titre.

However, irrespective of the results of tests at birth or even at six weeks, some infants develop very high titres of Hb<sub>s</sub>Ag at 3 to 4 months of age. Of 112 infants between 3 months and 2½ years of age (mean 10.7 months), 16 (14.2%) have very high titres. There is a marked ethnic difference in these 'carrier' infants: most of the antigen positive mothers are Asians from Pakistan, India, and Bangladesh (56%); the Chinese and Afro-Caribbean mothers make up 11% each, and the Europeans 24%; but nine of the infants with high Hb<sub>s</sub>Ag titre are Chinese (56%), four Afro-Caribbeans (25%), only three are Asians (19%), and there are no 'carrier' Europeans. All these infants are clinically healthy, but the mean transaminase levels in the antigen positive group are two to three times that of the antigen negative and a normal control group of infants.

Vertical transmission appears to be an important factor in the maintenance of hepatitis B virus in the Chinese and Afro-Caribbean population but not in the Caucasians.

#### Tumour staging in colorectal cancer

C. B. WOOD, C. R. GILLIS, AND L. H. BLUMGART (*University Department of Surgery, Royal Infirmary, Glasgow*) Staging classifications for colorectal cancer in current use are based on transmural spread of tumour and lymphatic involvement. However, they often do not take account of local tumour invasion of adjacent structures or even distant metastases.

We have prospectively studied 386 patients with large bowel cancer followed for up to 3½ years. Two hundred and eleven patients had Dukes B or C1 tumours. Those patients with mobile primary tumours and no distant metastases showed no significant difference in survival despite the presence of lymph node metastases. Where local invasion had occurred, survival time was decreased but was not related to lymph node status. Similarly, patients with distant metastases had a poor prognosis but survival was not altered by lymphatic involvement.

Thus, lymph node spread has not been an important determinant of survival

within the follow-up period. However, local tumour invasion and distant metastases were major prognostic factors. We propose a new staging classification based on these factors.

#### Peptic ulcer in renal failure

C. C. DOHERTY, F. A. O'CONNOR, K. D. BUCHANAN, J. M. SLOAN, J. E. S. ARDILL, AND MARY G. MCGEOWN (*Renal Unit, Belfast City Hospital and Department of Medicine, Royal Victoria Hospital*) Attitudes differ regarding management of peptic ulcer in the patient with renal failure. We therefore studied the pathophysiology of ulcer disease in uraemic patients, in order to evolve a logical approach to treatment.

Fifteen of 31 haemodialysis patients had pyloroduodenal ulceration (48%) and gastric acidity (basal and peak) in haemodialysed patients was significantly higher than in patients with untreated chronic renal failure. The distribution pattern of peak acid output in uraemic patients was found to be abnormal, with an increased proportion of acid hypo-secretors (22%) as well as hypersecretors (28%). Three patients with previous duodenal ulceration had atrophic gastritis with hypo or achlorhydria.

The upper limit for fasting plasma gastrin in this laboratory is 125 pg/ml. Thirty-one of 41 uraemic patients had values above this level, and eight were greater than 500 pg/ml. Six of these eight had atrophic gastritis with hypochlorhydria but the remaining two had acid hypersecretion and severe ulcer disease.

Peptic ulceration is therefore unusually frequent in uraemic patients and differs in some aspects from conventional ulcer disease. It is predominantly duodenal, and gastric hyperacidity and fasting hypergastrinaemia occur more commonly (47% and 73% respectively) than in ordinary duodenal ulcer (DU). The finding of atrophic gastritis in association with previous DU has important implications. Many dialysis centres advise prophylactic acid-lowering surgery when there is a definite history or radiological evidence of DU<sup>1,2</sup>, and this would obviously be totally illogical in those with atrophic gastritis.

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<sup>2</sup>Spanos, P. K., Simmons, R. L., Ratazzi, L. C., Kjellstrand, C. M., Buselmeier, T. J., and Najarian, J. S. (1974). Peptic ulcer disease in the



transplant recipient. *Archives of Surgery*, 109, 193.

### Evidence for a mycobacterial aetiology of Crohn's disease

W. R. BURNHAM, J. L. STANFORD, AND J. E. LENNARD-JONES (*St. Mark's Hospital, City Road, London and The School of Pathology, Middlesex Hospital, London*) Mesenteric lymph nodes taken at laparotomy from 27 patients with Crohn's disease, 13 with ulcerative colitis, and 11 controls have been cultured on Lowenstein-Jensen and hypertonic Sauton media. After eight months, one culture of Crohn's disease tissue grew a mycobacterium, subsequently indentified as a strain of *M. kansasii* (1129). Tuberculin-type skin tests, using a reagent prepared from this organism and another prepared from *M. tuberculosis*, have been performed. Eighteen of 40 patients but only 10 of 50 controls were positive to 1129 ( $P < 0.05$ ). Conversely, 40 of 56 controls but only 22 of 54 Crohn's disease patients were positive to *M. tuberculosis* ( $P < 0.05$ ). Among tuberculin positive subjects, 12 of 16 patients with Crohn's disease and nine of 36 control subjects, gave a positive reaction to 1129 ( $P < 0.005$ ).

Twenty-two of the 27 Crohn's disease cultures, seven of 13 colitis cultures but only one of 11 control cultures grew organisms during six months' incubation; these may be cell wall deficient mycobacteria.

These results suggest a mycobacterial aetiology of Crohn's disease which would be compatible with the published data on the transmissibility of inflammatory bowel disease<sup>1,2,3</sup>.

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#### SMALL BOWEL

### Adaptation of the shortened gut: greater initial response to resection than to bypass

R. C. N. WILLIAMSON, F. L. R. BAUER, AND R. A. MALT (introduced by Professor D. JOHNSTON) (*Surgical Services, Massachusetts General Hospital and Department of Surgery, Harvard Medical School, Boston,*

*Massachusetts 02114, USA*) Both excision and exclusion of the jejunum expose the distal bowel mucosa to higher luminal concentrations of food and gastroduodenal secretions<sup>1</sup>. Other possible factors involved in the control of intestinal adaptation were tested in rats ( $N = 114$ ) submitted to 50% proximal small bowel resection or bypass.

Within 48 hours, both operations increased RNA and DNA contents in ileal mucosa by 20-52% over values in control animals undergoing jejunal transection (differences,  $P = 0.05$  to  $0.001$ ). At one week, persistent rises in nucleic acids (35-90%:  $P < 0.005$ ) were accompanied by taller villi and deeper crypts (26-58%:  $P < 0.01$ ). In every variable at both times, increases were generally greater after resection than after bypass ( $P = 0.05$  to  $0.001$ ). DNA specific activity after <sup>3</sup>HTdR remained raised by 43% ( $P < 0.005$ ) one week after resection, despite the substantial increase (73%) in total DNA, indicating progressive hyperplasia. By one month, however, values after resection were equalled by those after bypass. Modest colonic hyperplasia occurred after proximal enterectomy alone.

The provision of a richer chyme to the ileum by proximal enteric bypass did not reproduce the early proliferative response of the mucosa to proximal enterectomy. Humoral factors<sup>2</sup> may also contribute to the rapidity and intensity of compensatory intestinal hyperplasia.

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### Is prolactin trophic to the intestine?

E. MULLER, T. BATES, D. SAMPSON, AND R. HERMON DOWLING (*Guy's Hospital and Medical School, London*) The intestinal mucosal hyperplasia and enhanced absorption of lactation<sup>1</sup> could, theoretically, be due to an enterotrophic effect of prolactin<sup>2</sup>, as the adaptive changes develop equally in isolated Thiry-Vella loops as intact intestine<sup>3</sup>. We therefore studied jejunal and ileal histomorphometry, mucosal wet weight, protein, and DNA in two groups of hyperprolactinaemic rats: (1) perphenazine treated (five virgin females given 5 mg.kg BW<sup>-1</sup>.day<sup>-1</sup>) subcutaneously for seven weeks; (2) pituitary

transplantation (three weeks after four renal subcapsular autotransplants/rat), their corresponding controls: (3) six solvent-injected, pair-fed rats; (4) adipose tissue transplantation ( $n = 6$ ), and compared the results in (5) six normal, weight-matched controls, and (6) five lactating rats (14th day).

The results showed jejunal villus height to be increased from  $344 \pm \text{SEM } 36 \mu\text{m}$  in controls to  $568 \pm 29$  during lactation, crypt depth from  $144 \pm 9$  to  $160 \pm 14$ , mucosal wet weight from  $30 \pm 2 \text{ mg/cm}$  to  $63 \pm 2$ , and protein from  $4.15 \pm 0.36 \text{ mg/cm}$  to  $6.93 \pm 0.2$  with comparable (17 to 96%) increases in the ileum. However, in spite of radioimmunoassay confirmed hyperprolactinaemia in the perphenazine treated and pituitary transplanted rats ( $169 \pm 20 \text{ ng/ml}$ ) compared with  $49 \pm 8$  in controls) there were no intestinal adaptive changes and the indices of mucosal mass actually fell slightly from 3 to 32% in jejunum and 0 to 22% in ileum.

We conclude that prolactin is not trophic to the intestine and that hyperprolactinaemia cannot explain the intestinal adaptation of lactation.

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### Structure and function of the mouse small intestine after infection with *Schistosoma mansoni*

P. B. VENGESA AND H. J. LEESE (introduced by G. WATKINSON) (*Department of Biology, University of York, York*) It is estimated that 200 million people suffer from bilharzia, also known as schistosomiasis, which is caused by parasites of the schistosome species. Although diarrhoea is a symptom of this condition, very little is known of the structure and function of the infected small intestine. We have, therefore, studied the effects of acute *Schistosoma mansoni* infection on the absorptive capacity of the small intestine of white mice, and also examined the structure of the gut under the light and electron microscope. Most of the work on absorption was carried out using an *in*

*in vitro* luminal perfusion apparatus. The results indicated a striking impairment in the transport of D-glucose, 3-O-methyl glucose, sorbitol, and fluid, in mice seven weeks post-infection. Kinetic analysis of the glucose transport data suggested a reduction in the number, rather than the affinity of the sugar absorptive sites. These findings correlated with the appearance of the villi which, in the infected animals, were swollen, eroded, and exhibited lesions and disruptions around their apices. The villous surface was also indented with deep sulci and covered with pronounced strands of mucous.

#### Elemental diet enhances the enteropathy of parasite infection in mice

ANNE FERGUSON, GILLIAN PAUL, T. T. MACDONALD, AND R. F. A. LOGAN (*Gastrointestinal Unit, Western General Hospital, Edinburgh*) We have reported that mice reared on the elemental diet Vivonex (Eaton Labs) will survive for months but are lighter than mice reared on a normal diet, have impaired antibody-forming capacity, and have fatty livers<sup>1,2</sup>. The effects of this elemental diet (ED) on intestinal histology of mice have now been examined; normal diet (ND) and ED mice have similar villus-crypt architecture, lamina propria cellularity, and intra-epithelial lymphocyte counts. In ND mice, infection with either *Giardia muris* or *Nippostrongylus brasiliensis* caused crypt hyperplasia and changes in intestinal lymphoid cells; in ED mice, significantly greater crypt hyperplasia, and villus atrophy, were produced by these parasite infections.

Three possible explanations for the enhanced enteropathy of parasites in animals eating Vivonex will be discussed: the aberrant immune capacity of such animals; sluggish intestinal motility; or improved nutrition of the parasites themselves.

Elemental diets should be used with caution in patients likely to have intestinal parasite infections—for example, children with marasmus.

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#### Digestive myoelectric response to food

D. WINGATE, HILARY THOMPSON, E. PEARCE, AND ANNE DAND (*Gastroenterology and Endocrinology Units, and Departments of Physiology and Experimental Surgery, London Hospital Medical College, London*) Duodenal, jejunal and ileal electrical activity was recorded for two hours before and four hours after a mixed meal in seven studies on dogs with implanted serosal electrodes. Recorded spike activity was analysed and measured during high-speed tape replay<sup>1</sup>. Serial measurements of plasma insulin and gastrin were undertaken in four out of seven studies. Irregular spike activity replaced fasting patterns at all three sites within minutes of feeding. Feeding induced a significant ( $P < 0.01$ ) increase in overall spike activity in jejunum and ileum, but not duodenum. Except in the duodenum, post-prandial peaks in spike activity were not synchronous with plasma hormone peaks. There was a consistent and sustained fall ( $P < 0.01$ ) in the gastric basic electrical rhythm after food, but the duodenum was not affected. Comparison of these results with 44 studies of CCK and pentagastrin infusion, suggests that neither peptide accounts for the response to food in the mid and distal small intestine<sup>2</sup>. It seems that the canine motor response to food is either mediated by other humoral agents—our studies do not support insulin<sup>3</sup> as a candidate—or under neural control, or both.

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#### Similar—but different: the myoelectric response to cholecystokinin and pentagastrin in the conscious dog

D. WINGATE, HILARY THOMPSON, ELIZABETH PEARCE, AND ANNE DAND (*Gastroenterology Unit, and Departments of Experimental Surgery and Physiology, London Hospital Medical College, London*) New methods<sup>1,2</sup> of recording and analysing digestive myoelectric activity that permit, for the first time, quantitative measure-

ments of spike activity have been used to study the effects of gastrin and CCK on duodenal, jejunal, and ileal myoelectric activity in conscious fasted dogs. Each of four dogs received six infusions of pentagastrin (0.125-4  $\mu\text{g}/\text{kg}/\text{h}$  intravenously) and five infusions of cholecystokinin (Karolinska) (0.125-2 U/kg/h intravenously); each two hour infusion was preceded and followed by a two hour saline infusion. Both peptides abolished duodenal and jejunal migrating complexes (MMC), substituting irregular spiking activity, but had little effect on ileal MMCs. This was a threshold effect rather than linearly dose-related. Cholecystokinin—but not pentagastrin—significantly ( $P < 0.001$ ) increased jejunal spike activity; but, apart from this, the main effect of the peptides was on the disorganisation of fasting activity in the duodenum and jejunum. There was a dose-related acceleration of the gastric pacemaker ( $P < 0.001$ ) and the duodenal pacemaker ( $P < 0.01$ ) in response to pentagastrin; cholecystokinin was without effect. We conclude that cholecystokinin has myoelectric effects which are similar to<sup>3</sup>, but not identical with its structural analogue; the failure of both peptides to abolish distal fasting (peristaltic) patterns suggests a possible explanation for transit disturbances after denervating surgical procedures.

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#### Glucagon stimulates intestinal motor activity

D. WINGATE, D. MORRIS, AND P. THOMAS (*Gastroenterology and Endocrinology Units, and Departments of Experimental Surgery and Physiology, London Hospital Medical College, London*) We studied the effect of exogenous glucagon on myoelectric activity in the canine small intestine, both in the isolated vascular-perfused organ, and in the conscious fasted dog with implanted serosal electrodes. Duodenal—but not jejunal or ileal—inhibition was seen with 1 mg rapid intravenous doses,

supporting the accepted view of glucagon as an inhibitor<sup>1</sup>. By contrast, slow infusion (0.25-1.0 mg/2 h) stimulated all levels of the small bowel, abolishing fasting complexes and inducing irregular spiking. The increase in jejunal spike activity was greater than we have encountered with any other agent tested. Serial assays of plasma insulin during the infusions did not support the hypothesis that insulin is the active agent<sup>2</sup>; moreover, insulin had no effect on the isolated tissue, whereas glucagon (50-100 µg) induced a brisk motor response, implying a direct action of the peptide on the smooth muscle. We conclude that current views on the intestinal role of glucagon are based on pharmacological rather than physiological studies. The widespread distribution of enteroglucagon, and the resemblance between the response to slow glucagon infusion and the response to food<sup>3</sup>, suggest the possibility of a major role for glucagon in the regulation of digestive motor activity.

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- <sup>3</sup>Wingate, D. L., Thompson, H. H., Pearce, E. A., and Dand, A. (1977). Quantitative analysis of the effect of feeding on canine intestinal myoelectric activity. *Gastroenterology*, **72**, 1151.

#### Identification of stem cells in the rat and human intestinal mucosa

N. A. WRIGHT, H. AL-DEWACHI, D. R. APPLETON, AND A. J. WATSON (*Departments of Pathology and Medical Statistics, University of Newcastle upon Tyne*) During treatment with abdominal radiotherapy and systemic cytotoxic chemotherapy, intestinal side-effects can be a limiting factor in treatment; consequently, it becomes important to identify those cells responsible for repopulating the intestinal crypts after death of proliferating cells, to design treatment regimes with maximal bowel sparing action.

Detailed analysis of proliferation rates in the rat jejunal crypt showed that a small subpopulation of basally situated cells have long cell cycle times, between 20 and 30 h, compared with 11 h in the remainder of the crypt. These cells would be expected to survive phase specific insult such as irradiation, and be available for crypt repopulation.

This hypothesis was tested by giving

rats a large dose (1840 mg/kg) of hydroxyurea, an agent which kills proliferating cells in DNA synthesis. The recovery sequences in the crypt were initiated by increased cell production rates in basal crypt cells produced by a decrease in their cell cycle time, which led to repopulation of the depleted crypt.

Using metaphase arrest methods with vincristine, we have shown that long cycling basal crypt cells also occur in man. We propose that slowly proliferating basal crypt cells are important candidates for the role of stem cells in human and rodent intestinal mucosa.

#### Mechanism of action of prednisolone on the absorptive-digestive functions of the rat small intestine

J. SCOTT, R. M. BATT, AND T. J. PETERS (*Department of Medicine, Royal Postgraduate Medical School, London*) Corticosteroids have been used successfully to treat patients with chronic intestinal disease. Previous studies<sup>1</sup> have shown that in the rat oral administration of pharmacological doses of prednisolone-21-phosphate, 0.75 mg/kg body weight daily for seven days, produces an approximately 50% increase in the absorptive and digestive capacities of the jejunal enterocytes. These effects occurred without any alteration in the size of the cell population or the cell kinetics and it is postulated that the corticosteroid directly affects the mature enterocyte.

Analytical subcellular fractionation studies<sup>2</sup> have demonstrated enhanced enzyme activities associated with the brush border and an increase in the modal density of this organelle in the steroid-treated cells. This is consistent with an increase in the content of both enzyme and carrier protein in the brush border membrane and suggests a selective effect of corticosteroid on this organelle.

The total RNA content of the prednisolone-treated enterocytes was approximately twice that of the control cells. Subcellular fractionation has demonstrated that a large proportion of this increase is associated with a distinct particulate component not present in the control cells. Measurements of free and membrane-bound polysomes have shown this to be due to a proliferation of the rough endoplasmic reticulum. This indicates a specific effect of prednisolone on the protein synthetic process for membrane components of the cell such as the brush border. Direct measurements of *in*

*vitro* incorporation of <sup>14</sup>C tyrosine into cell protein<sup>3</sup> showed that enterocytes from the steroid-treated animals synthesised protein at an enhanced rate compared to the control.

These studies suggest that the beneficial effects of prednisolone on the small intestinal mucosa are due to an enhanced rate of synthesis of specific proteins, particularly those associated with the brush border, probably mediated at the levels of both transcription and translation.

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#### Action of prednisolone on the small bowel mucosa

H. AL-DEWACHI, N. A. WRIGHT, D. R. APPLETON, AND A. J. WATSON (*Departments of Pathology and Medical Statistics, University of Newcastle upon Tyne*) Adrenocortical steroids have found use in the treatment of coeliac disease and earlier work<sup>1</sup> has suggested that these drugs can decrease crypt cell populations; thus an inhibitory action on the hyperproliferative coeliac mucosa appears probable. However, recent studies<sup>2</sup> have failed to show such an action in the rat, and Tutton<sup>3</sup> has claimed that prednisolone stimulates crypt cell proliferation.

The effect of single and multiple doses of prednisolone on the rat jejunal crypt was studied, using autoradiographic and stathmokinetic techniques. Single injections of prednisolone (2.5 mg/kg) depressed both flash thymidine labelling and mitotic indices, shown to be due to a decreased cell production rate; seven days after prednisolone a compensatory hyperplastic response, with a raised cell production rate, was demonstrated.

Multiple daily injections of prednisolone (1 mg/kg) produced a sustained decrease in labelling and mitotic indices, lasting as long as injections were continued (seven days). Crypt cell production rates were also decreased over this period.

We conclude that prednisolone depresses cell proliferative rates in rat jejunal mucosa. Consequently, in addition to its anti-inflammatory role in coeliac disease, the drug may also act by inhibition of cell division.



## References

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<sup>2</sup>Batt, R. M., and Peters, T. J. (1976). *Clinical Science and Molecular Medicine*, 50, 511.  
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## CLINICAL MEDICAL

**Hepatitis B: absence of transmission by gastrointestinal endoscopy**

D. B. L. MCCLELLAND, C. J. BURRELL, R. W. TONKIN, AND R. C. HEADING (*Departments of Therapeutics and Bacteriology, University of Edinburgh*) After upper gastrointestinal endoscopy with biopsy of a patient who was later discovered to be a carrier of both hepatitis B surface antigen (HBsAg) and HBeAg, 38 patients were examined with the same endoscope over a period of 15 days. Nineteen of these patients were subjected to biopsy. Patients were followed up and two blood samples obtained at approximately four-month intervals. There was no evidence of hepatitis in any patient, no patient developed HBs antigenaemia, and no patient acquired antibody to the HBsAg after examination.

*In vitro* experiments were then conducted in which an endoscope and biopsy forceps were deliberately contaminated with gastric juice containing inactivated <sup>125</sup>I HBsAg to evaluate the instrument cleaning procedures in routine use. More than 200 µl of contaminated gastric juice was recovered from the instruments after routine cleaning, indicating that the procedures are not effective.

Although the risks of transmission of hepatitis B infection during endoscopy appear to be smaller than expected, our instrument cleaning procedures have been modified and will be described.

**Acute lead poisoning—an unusual cause of hepatitis**

A. D. BEATTIE, P. MULLIN, R. BAXTER, AND M. R. MOORE (*Southern General Hospital, Victoria Infirmary, and University Department of Materia Medica, Stobhill Hospital, Glasgow*) Six patients, aged 17 to 25 years, obtained lead and opium pills which had been stolen from retail pharmacists in 1973 and 1977. They crushed them, suspended them in water, and injected them intravenously. Two of the patients developed malaise and jaundice within three days and one died of acute hepatic failure. The other survived for two

months but died after a prolonged neuropathy despite adequate chelation. The remaining four patients were less severely ill and blood tests done several weeks after ingestion of the pills showed raised alkaline phosphatase and aspartate transaminase. Necropsy or biopsy specimens were obtained from all cases and showed acute hepatitis in the first fatal case and resolving hepatitis in the remaining five. Liver lead levels were grossly raised in every case.

Chronic lead poisoning in the industrially exposed or in children with pica does not usually affect liver function. Goyer and Rhyme<sup>1</sup> reported impaired respiratory and phosphorylative function in the livers of lead intoxicated animals. It seems likely that the livers of patients with chronic lead poisoning are able to withstand this insult, whereas in the cases described here the overwhelming dose of lead was sufficient to cause hepatic failure.

## Reference

- <sup>1</sup>Goyer, R. A., and Rhyme, B. C. (1973). Pathological changes in lead poisoning. *International Review of Experimental Pathology*, 12, 1.

**Comparison of features of alcoholic liver disease**

A. M. CONNELL, D. WEIR, O. FITZGERALD, W. McDONALD, M. WHELTON, C. MCCARTHY, J. KENNEDY, M. FAIRMAN, AND C. BALL (*Departments of Medicine, University Hospitals, Cincinnati, Ohio and Ireland*) The severity and prevalence of alcoholic liver disease seems to be greater in the US than in Great Britain and Ireland. This is usually attributed to greater alcohol consumption in the US, although the role of dietary deficiency has long been debated. A cross-sectional prospective study of patients with alcoholic liver disease was undertaken simultaneously in Cincinnati and Dublin, Cork, and Galway, Ireland. Dieticians and residents carefully assessed clinical data, alcohol consumption, and diet. One-hundred-and-seventy-four patients ('Study Group') (Cincinnati: male (67), female (30), Ireland: male (55), female (22)) all of whom had a liver biopsy, were compared with a control group of 819 patients (Cincinnati, 216, Ireland, 603). Laboratory and clinical data were condensed into a single index of clinical severity termed 'Clinical Score'. The Clinical Score (mean ± SE) in the Cincinnati study group was much higher (male 6.6 ± 0.4, female 5.7 ± 0.7) than in the Irish (male

3.1 ± 0.3, female 3.8 ± 0.6,  $P < 0.05$ ). Fibrosis, regeneration, portal inflammation, fatty change, hepatocellular necrosis, and piecemeal necrosis were graded in one centre on a scale between 0 and 4, and from these features an overall 'Pathscore' was developed. The Pathscore was also higher among the Americans (male 14.1 ± 0.9, female 15 ± 1.2) than the Irish (male 5.4 ± 0.6, female 8.5 ± 1.4,  $P < 0.05$ ). Significant correlations between alcohol consumption and pathological damage were more prominent in the Irish patients. The Cincinnati study group consumed less food than their controls and correlations between dietary factors and pathological features were more significant in this group. Milk, animal fat, and protein were associated with less fibrosis, regeneration, and fatty change. In summary, the greater severity of liver disease in the USA cannot be explained in terms of alcohol consumption only and dietary factors appear to be important.

**Can we believe the figures? Deaths from cirrhosis and hospital prevalence**

A. N. HAMLYN AND O. JAMES (*Department of Medicine, Royal Victoria Infirmary, Newcastle upon Tyne*) Suggestions<sup>1</sup> that the incidence of alcoholic cirrhosis has been hitherto underestimated have prompted a survey of mortality for the latest available year, 1975.

The number of death entries for England and Wales was 1835 (0.3% of total mortality). The proportion of all alcoholic cirrhotic deaths was 22% compared with 11% in 1971. Estimated proportion of deaths attributable to various causes was as follows: alcoholic cirrhosis—males (M) 30.3%, females (F) 12.5%; primary biliary cirrhosis—M 0.8%, F 8.6%; cryptogenic cirrhosis—M 8.3%, F 11.3%; active chronic hepatitis—M 5.8%, F 7.7%; secondary biliary cirrhosis—M 2.9%, F 2.3%; miscellaneous causes—M 5.7%, F 7.8%. The largest category was cirrhosis, cause unspecified—males 46.2%, females 49.8%. In a 1:4 unstratified random sample of the non-alcoholic deaths 2.9% of men and 4.5% of women had been in 'alcoholic' occupations. The estimated post mortem rate was 59.2% for males and 54.4% for females. Comparison with a local series of cirrhotic patients and published experience<sup>2,3</sup> from elsewhere leads to the conclusions that (1) specified forms of cirrhosis, such as PBC, were certified more frequently than before, (2) alcoholic cirrhosis deaths were certified

twice as frequently as in 1971, (3) there was a disparity between diagnostic and death certifying habits over the period studied, (4) a large proportion of unspecified cirrhosis deaths together with occupational clues suggests significant under-representation in official figures of alcoholic liver disease.

#### References

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<sup>2</sup>Jain, S., Paton, A., and Wansborough-Jones. (1973). Cirrhosis in Birmingham. *Midland Medical Review*, 9, 13-16.  
<sup>3</sup>Hamlyn, A. N., Brown, A. J., Sherlock, S., and Baron, D. N. (1975). Casual blood ethanol estimations in patients with chronic liver disease. *Lancet*, 2, 345-348.

#### Estimation of the sodium content and neutralising capacity of some commonly used antacids

R. E. BARRY AND J. FORD (*Department of Medicine, University of Bristol, Bristol Royal Infirmary*) Patients suffering from hepatic failure, renal failure, and heart failure commonly require treatment regimes involving strict sodium restriction. The incidence of dyspeptic symptoms in these conditions is high, so that they are frequently treated concomitantly with antacids. Several authors have warned that some antacids contain quite large quantities of sodium sufficient to complicate seriously any therapeutic regime requiring salt restriction.

Information on the theoretical sodium content of *BP* and *BNF* preparations is readily available but only one commercial antacid preparation available in the UK (June 1977) states the sodium content on the statutory *Product Data Sheet*. In order to make this information freely available, we have measured the sodium content of 13 liquid and 12 tablet antacids which are in common use in our health district. The neutralising capacity of each antacid was also measured by a method based on that of Fordtran *et al.*<sup>1</sup> so that a comparison of *in vitro* neutralising capacity and sodium content can be made.

For liquid antacids, sodium content varied from 225 mg to <1 mg per 10 ml dose. Based on manufacturer's maximum recommended dose, daily sodium consumption from commercial antacids may vary from 5 mg/day (Asilone suspension) to 1030 mg/day (Gaviscon liquid), whereas consumption from *BP* preparations may vary from 2 mg/day (Magnesium Hydroxide Mixture, *BP*) to >1300 mg/day

(Magnesium Carbonate Mixture *BP*). For commercial antacids, neutralising capacity of a 10 ml dose at 2 h, 37°C, varied from 314 ml 0.1N HCl (Asilone suspension) to only 54 ml 0.1N HCl (Gaviscon liquid).

For tablet antacids, sodium content varied from 32 mg/tablet (Gaviscon) to <1 mg/tablet (Prodexin, Maalox, Titralac) giving a daily sodium consumption of <8 to 256 mg/day. Neutralising capacity of the tablet antacids varied from 15 to 165 ml 0.1N HCl per tablet.

**Conclusion** The sodium content and neutralising capacity of some commonly used antacid preparations have been measured. The information obtained allows ready identification of those preparations which would seriously affect the treatment of patients requiring sodium restriction.

#### Reference

- <sup>1</sup>Fordtran, J. S., Morawski, S. G., and Richardson, C. T. (1973). *New England Journal of Medicine*, 288, 923-928.

#### Bacterial overgrowth without 'blind loop' a cause for malnutrition in the elderly

S. H. ROBERTS, E. H. JARVIS, AND O. JAMES (*Department of Medicine (Geriatrics) Newcastle General Hospital*) Malnutrition is frequent in the elderly and is often ascribed to 'poor diet'. Recently interest has increased in possible causes for malabsorption in old people<sup>1</sup>. Bacterial overgrowth is a recognised cause in those with jejunal diverticulosis<sup>2</sup>. We report five elderly patients without anatomical abnormalities of the small intestine in whom bacterial overgrowth was demonstrated by abnormal <sup>14</sup>C glycocholate breath tests.

All subjects presented with weight loss and debility. All had biochemical evidence of osteomalacia. Other abnormalities were steatorrhoea (two), abnormal Dico-pac (four), macrocytic anaemia (four), low B12 (two), low folate (one).

Normal jejunal biopsies and <sup>75</sup>Se selenomethionine pancreatic scans made other causes of malabsorption less likely. Despite hospital treatment no patient improved until broad spectrum antibiotics were given. This led to weight gain, dramatic improvement in general health, and maintenance of normal haematological and biochemical indices. Associated factors contributing to bacterial contamination were achlorhydria (three) and a grossly delayed small bowel transit of barium (one).

**Conclusion** Bacterial contamination of

an anatomically normal small intestine may be a common cause of malabsorption and malnutrition in elderly patients, particularly in association with achlorhydria. It is notable that diarrhoea was not prominent in these patients. Antibiotic treatment brought marked symptomatic and nutritional improvement.

#### References

- <sup>1</sup>Price, H. L., Gazzard, B. G., and Dawson, A. M. (1977). Steatorrhoea in the elderly. *British Medical Journal*, 1, 1582.  
<sup>2</sup>Donaldson, S. F. (1973). Blind loop syndrome. In *Gastrointestinal Disorders*, p. 927. Edited by M. H. Slesinger and J. S. Fortran. Saunders: London.

#### Influence of metronidazole and neomycin on colonic microflora in healthy volunteers

Y. ARABI, F. DIMOCK, D. W. BURDON, J. ALEXANDER-WILLIAMS, AND M. R. B. KEIGHLEY (*The General Hospital, Birmingham*) Metronidazole (M) has been reported to reduce the anaerobic flora of the small bowel<sup>1</sup> but a reduction in colonic bacteria has been reported only when M has been used with either neomycin (N) or kanamycin<sup>2,3</sup>.

The aim of this study has been to determine the influence of M and N on colonic microflora in volunteers taking a normal diet. Daily viable counts of fresh stool were measured before, during and one week after a five day course of antibiotic. Subjects received the following antibiotics: group 1: N + M, (n = 9); group 2: M alone (n = 4); group 3: N alone (n = 4). The dose of N was 1 g eight hourly and of M, 200 mg eight hourly. In group 1 three days after treatment there was a mean reduction of total aerobes from 10<sup>6</sup> to <10<sup>1</sup> orgs/ml and counts of anaerobes were reduced from 10<sup>7</sup> to 10<sup>1</sup> orgs/ml. In most cases the flora was still reduced three days after finishing the antibiotics. In group 2 there was no influence on the total number of aerobes or anaerobes. In group three there was only a moderate reduction of aerobes and no influence on anaerobes.

These results indicate that M alone has no influence on colonic microflora but that the addition of N is responsible for a profound reduction of both aerobic and anaerobic organisms. These findings could explain the disappointing results of treatment with M in the management of blind loop syndromes and Crohn's colitis.

#### References

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<sup>2</sup>Goldring, J., Scott, A., McNaught, W., and Gillespie, G. (1975). Prophylactic oral antimicrobial agents in elective colonic surgery. *Lancet*, 2, 997-999.

<sup>3</sup>Arabi, Y., Dimock, F., Burdon, D. W., and Keighley, M. R. B. (1977). Influence of bowel preparation on colonic microflora. *British Journal of Surgery*. (In press.)

### Serial light and electron microscopy of intestinal mucosa in Whipple's disease

P. MILLS, I. MORE, A. DICK, R. HOLDEN, AND G. WATKINSON (*Departments of Medicine and Pathology, Western Infirmary and Southern General Hospital, Glasgow*) A 39 year old man developed gross malabsorption associated with rectal bleeding, purpura, pyrexia, finger clubbing, and skin pigmentation. Jejunal biopsy confirmed the diagnosis of Whipple's disease with villous stunting, infiltration of the lamina propria with macrophages containing PAS +ve staining granules and free rod-shaped bacteria seen at electron microscopy.

He was treated with parenteral penicillin and streptomycin for three weeks, followed by oral deoxycycline 100 mg once daily which he is still taking. He has made a rapid and full clinical recovery.

Jejunal biopsies were carried out at six weeks, then at three monthly intervals; seven months after starting therapy the biopsy appears little changed by light microscopy.

Electron microscopy initially showed many free bacteria and bacteria within foamy macrophages in varying stages of digestion in phagocytic vacuoles. Six weeks later fewer bacteria were present and most were in a state of degeneration. At four months there were no free bacilli and the still abundant macrophages contained phagocytic vacuoles in a late stage of digestion.

We would suggest that electron microscopy is important in diagnosing and assessing response to treatment in cases of Whipple's disease. Light microscopy of jejunal biopsies may remain unchanged for long periods after treatment<sup>1</sup>.

#### Reference

<sup>1</sup>Trier, J. S., et al. (1965). *Gastroenterology*, 48, 684.

### Survey of protein nutrition in inflammatory bowel disease—a rational basis for nutritional therapy

I. PICKFORD, G. L. HILL, R. L. BLACKETT,

AND J. A. BRADLEY (*University Department of Surgery, The General Infirmary, Leeds*) Malnutrition, hypoproteinaemia, and in particular hypoalbuminaemia are well-recognised problems in ulcerative colitis and Crohn's disease. However, no survey exists to show the incidence of protein malnutrition in inflammatory bowel disease (IBD).

Seventy-four unselected patients were studied and allocated to one of six categories: ileostomy (16), remission (15), elective surgery (12), acute attack (12), urgent surgery (10), and post-surgical complications (nine).

To assess protein nutrition, per cent weight loss, arm muscle circumference, haemoglobin, plasma albumin, plasma transferrin, and plasma pre-albumin were measured. Comparison was then made with the values obtained for 15 healthy controls.

In the whole group (excluding ileostomy patients who were not significantly different from the controls) there was a significant lowering of haemoglobin ( $14.7 \pm 1.4$  g/dl cf.  $11.9 \pm 1.9$  g/dl,  $P < 0.001$ ); albumin ( $43.2 \pm 2.2$  g/l cf.  $40.5 \pm 5.7$  g/l,  $P < 0.05$ ); transferrin ( $283 \pm 25$  mg/100 ml cf.  $230 \pm 89$  mg/100 ml,  $P < 0.025$ ) and pre-albumin ( $29.5 \pm 4.2$  mg/100 ml cf.  $23.7 \pm 12.0$  mg/100 ml,  $P < 0.05$ ) and there was an overall fall of  $10.0 \pm 9.6\%$  in body weight.

This lowering was least in the patients in remission (10-20%) and greatest in the urgent surgery group (50-60%) and those with post-surgical complications (> 70%). Of the nine patients in this group seven required intravenous feeding and two died. There was no significant difference between the patients with Crohn's disease and those with ulcerative colitis.

It is concluded that patients undergoing urgent surgery for IBD require nutritional support and that these findings may help to explain some of the severe post-operative complications encountered.

### Effects of marginal protein malnutrition on parasitic infection of the intestine

A. M. TOMKINS, K. MADI, AND B. M. OGILVIE (*Clinical Nutrition and Metabolism Unit, Department of Human Nutrition, London School of Hygiene and Tropical Medicine, London and National Institute for Medical Research, London*) Hooded rats fed an adequate diet (protein energy: total metabolisable energy (NDP:E) 0.1) (group I) infected with *Nippostrongylus brasiliensis* (Nb) (500 larvae subcutaneously) when 3

weeks old developed villous atrophy after seven days (villus/crypt ratio  $1.05 \pm 0.26$ ). Mucosal regeneration started by 14 days (V/C  $1.64 \pm 0.24$ ) as worms were eliminated, egg counts decreased ( $65.5 \times 10^3 \rightarrow 5.5 \times 10^3$ /g faeces) and mucosal mast cells increased ( $118 \pm 3.0 \rightarrow 333 \pm 39.3$  cells/10 V/C units). Growth was unimpaired.

A diet marginally deficient in protein (NDP:E, 0.068) produced normal growth in uninfected young rats but a colony fed over 12 generations produced low birth weight offspring<sup>1</sup> (group II). Worm clearance in these after Nb at 3 weeks was less efficient than in group I ( $364 \pm 49$  v.  $212 \pm 22$  remaining at 15 days). Neither did egg excretion decrease; mucosal mast cells failed to increase. Villous atrophy at seven days was less severe than in group I (V/C  $1.8 \pm 0.41$  v.  $1.05 \pm 0.26$ ) but infected animals weighed 31% less than uninfected controls suggesting that marginal protein deficiency limits both expulsion mechanisms and mucosal damage induced by Nb but changes are sufficient to precipitate malnutrition.

#### Reference

<sup>1</sup>Stewart, R. J. C., Preece, R. F., and Sheppard, H. G. (1975). Twelve generations of marginal protein deficiency. *British Journal of Nutrition*, 33, 233-253.

### INFLAMMATORY BOWEL

### Spectrum of hepatic dysfunction in inflammatory bowel disease

M. J. DEW AND R. N. ALLAN (*The Nutritional and Intestinal Unit, The General Hospital, Birmingham*) The aims of this study are to categorise the types of hepatic dysfunction in inflammatory bowel disease, to define the risk factors and thus provide a rational basis for clinical management. From among 520 patients with Crohn's disease, and 720 with ulcerative colitis (mean follow-up 13.0 years including sequential clinical and biochemical review) patients with serial alkaline phosphatase levels above 20 KA units of proven hepatic origin have been studied. This level is most closely related to significant liver disease<sup>1</sup>.

Fifty-seven patients with Crohn's disease and 44 with ulcerative colitis were studied and divided into subgroups which included transient perioperative changes, pericholangitis, cirrhosis, stenosing cholangitis, and bile duct carcinoma. Liver biopsy was performed in more than 60%.



Transient perioperative rise was common in Crohn's disease (44% vs 10%). This was often related to sepsis but not disease extent, duration, or type of resection. In contrast cirrhosis is much commoner in ulcerative colitis (22% vs 5%) and occurs only with total colitis. Stenosing cholangitis and bile duct carcinoma occurred almost exclusively in ulcerative colitis (27% vs 2%) and is associated with long-standing total disease. Drug therapy did not seem to induce hepatic dysfunction. The effect of defining these subgroups on clinical management will be discussed.

#### Reference

<sup>1</sup>Eade, M. N. (1970). Liver disease in ulcerative colitis. *Annals of Internal Medicine*, 72, 415-487.

#### Direct method of measuring faecal protein loss in patients with ulcerative colitis

N. A. BUCKELL, S. R. GOULD, M. A. HERNANDEZ, J. KOHN, J. E. LENNARD-JONES, J. POWELL-TUCK, P. G. RICHES, AND S. G. WELCH (*St Mark's Hospital, London and The London Hospital, Whitechapel, London, Supraregional Protein Reference Unit, Putney Hospital, London*) Isotopic techniques of measuring intestinal protein loss assume that the labelled protein is metabolised in the same way as endogenous protein and that the label remains bound to the protein. A simple direct method for measuring protein loss from the colon has been developed using a modification of the Ponceau-S dye technique<sup>1</sup>. Weighed aliquots are taken from 24 hour faecal collections, the protein is extracted in saline and the faecal debris is separated by centrifugation at 16 000 r.p.m. An aliquot of the supernatant is added to a standard solution of Ponceau-S dye in 3% trichloroacetic acid. The resulting suspension is thoroughly mixed, centrifuged, and the supernatant removed, thereby eliminating any discoloration caused by soluble faecal material. The dye-stained protein is redissolved in 0.8% sodium hydroxide and the amount of protein determined colorimetrically.

The method is highly reproducible and the recovery of known amounts of added albumin was  $99.5 \pm 12.6\%$  (SD). The method has been compared with the Kjeldahl technique and a highly significant correlation ( $r = 0.96$ ,  $p < 0.001$ ) found between the two methods.

Serial 24 hour faecal protein losses have been measured in 24 patients undergoing treatment for attacks of ulcerative colitis.

The losses ranged from 0.1 to 26.2 g in 24 hours. The protein loss correlated well with the clinical severity of the attack and a favourable response to treatment was associated with a reduction in the faecal protein loss. A significant inverse correlation between the faecal protein loss and the serum albumin concentration was demonstrated ( $r = -0.54$ ,  $p < 0.01$ ).

#### Reference

<sup>1</sup>Pesce, M. A., and Strande, C. S. (1973). A new micromethod for determination of protein in cerebrospinal fluid and urine. *Clinical Chemistry*, 19, 1265-1267.

#### Killer cell activity and numbers in inflammatory bowel disease

M. W. DRONFIELD AND M. J. S. LANGMAN (*Department of Therapeutics, City Hospital, Nottingham*) The results of colon cell cytotoxicity<sup>1</sup> and other studies<sup>2</sup> in inflammatory bowel disease (IBD) suggest that a killer (K) cell is involved in pathogenesis. We have, therefore, measured K cell activity by the lytic effect of peripheral blood lymphocytes on chromium <sup>51</sup>-labelled chick RBC's when incubated together with anti-chick RBC antibody in 35 patients with IBD and 11 controls.

When a fixed number of lymphocytes were added to the chick RBCs the percentage of RBC lysis, which expresses K cell activity, was only  $42.7 \pm 5.7$  (mean  $\pm$  SEM) in 12 patients with severe symptomatic IBD, compared with  $59.5 \pm 5.0$  in 10 patients with mild symptoms,  $68.6 \pm 2.9$  in 13 asymptomatic patients and  $72.4 \pm 2.1$  in 11 healthy controls.

Lymphocytes with temperature dependent binding of fluorescein labelled immunoglobulin may well be K cells, and this is supported by our finding that the proportion of such cells in the peripheral blood of normal people correlates well with K cell activity. By contrast, in symptomatic IBD more lymphocytes binding immunoglobulin in this way are detectable than would be expected from the K cell activity. We therefore conclude that symptomatic IBD patients have reduced K cell activity but that the numbers of circulating K cells are normal, their function perhaps being impaired by the action of circulating immune complexes<sup>3</sup>.

#### References

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required to lyse allogeneic colonic epithelia cells. *Gastroenterology*, 70, 171-176.

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#### Experiment to determine the active therapeutic moiety of sulphasalazine

A. K. AZAD KHAN, J. PIRIS, AND S. C. TRUELOVE (*Nuffield Department of Clinical Medicine and Department of Morbid Anatomy, Radcliffe Infirmary, Oxford*) Sulphasalazine (SASP) is of proven value in the treatment of ulcerative colitis but its mode of action is unknown. When taken by mouth, nearly all the dose reaches the colon intact and there it is split by the colonic bacteria into sulphapyridine (SP) and 5-aminosalicylic acid (5-ASA). The present experiment was devised in order to determine whether the therapeutic property of SASP is a function of the parent molecule or of one of these two principal metabolites. Retention enemas were prepared of SASP, SP, and 5-ASA and were administered to volunteer patients with sigmoidoscopic evidence of active ulcerative colitis. The experiment was conducted as a blind controlled therapeutic trial, each patient using one of the test enemas daily for a period of two weeks. Pronounced histological improvement was shown in approximately 30% of the patients receiving SASP or 5-ASA, whereas only 5% of the patients receiving SP showed such a change. It is concluded that the active therapeutic moiety of SASP is 5-ASA and that the SP functions as a carrier ensuring that the 5-ASA is liberated within the colon.

#### Levamisole in Crohn's disease—a double-blind controlled trial

E. WESDORP, P. T. A. SCHELLEKENS, R. WEENING, S. G. M. MEUWISSEN, AND G. N. J. TYTGAT (*Department of Medicine, Division of Gastroenterology, Wilhelmina Gasthuis, University of Amsterdam, and Laboratory for Experimental and Clinical Immunology, Amsterdam, The Netherlands*) We tested the hypothesis that levamisole, a non-specific immunostimulant, is beneficial to patients with Crohn's disease, who suffer from an impaired anamnestic cellular immune response<sup>1</sup>. Therefore 21 consecutive patients (six males and 15 females between 21-62

years) with active Crohn's disease entered a double-blind placebo-controlled study. None of the patients received immunosuppressive therapy. They were randomly allocated to either levamisole (11 patients) or placebo (10 patients) given in a dose of 2.5 mg/kg body weight on two successive days each week for three months. All patients were seen at the start and six and 12 weeks later, for physical examination, laboratory analysis (ESR, peripheral blood count, thrombocytes, serum albumin, immunoglobulin, lysozyme, C<sub>3</sub> and C<sub>4</sub> levels, and fecal fat and fecal Cr<sup>51</sup>Cl<sub>3</sub> protein loss) and for immunological investigation (cutaneous reactivity to PPD, varidase, trichophyton, candida and mumps; *in vitro* lymphocyte stimulation with phytohemagglutinin, a cocktail of the above skin antigens, and allogenic cells; determination of % T lymphocytes with the E rosette technique, granulocyte chemotaxis and phagocytosis). The Crohn's disease activity index<sup>2</sup> was used for clinical scoring.

The overall results of this study did not show any obvious improvement neither in clinical, nor in biochemical parameters. The pre- and post-activity index was 141.5 ± 75.9 versus 131.8 ± 71.3 in the placebo group and 83.1 ± 59.6 versus 79.9 ± 63.8 in the levamisole group. Only two placebo and one levamisole patients improved clinically and biochemically during the observation period. Neither was there a change in the extensively studied various immunological parameters. In particular the depressed skin reactivity was not influenced by levamisole.

This study therefore shows that levamisole, under the conditions of this protocol, was ineffective in ameliorating clinical, biochemical, and immunological parameters in patients suffering from Crohn's disease.

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#### Further studies of salicylazosulphapyridine metabolism in the treatment of ulcerative colitis

G. O. COWAN, K. M. DAS, AND M. A. EASTWOOD (Wolfson Laboratory, Gastrointestinal Unit, Western General Hospital,

Edinburgh) The value of salicylazosulphapyridine (SASP) in the treatment of ulcerative colitis is well established<sup>1</sup>. Successful treatment of ulcerative colitis coincides with a total serum concentration of sulphapyridine (SP) greater than 20 ug/ml<sup>2</sup>.

We have studied more patients with ulcerative colitis with continuing disease activity in whom the concentration of SP exceeds 20 ug/ml.

There were 64 out patients with ulcerative colitis receiving maintenance therapy with SASP and disease activity related to serum concentration of SP. Of 43 patients in remission, 32 had serum SP concentrations over 20 ug/ml. Of 21 patients with active disease 10 were for various reasons taking inadequate dosage of SASP, as indicated by low serum SP levels. Eleven patients with active disease and serum concentrations are over 20 ug/ml. Nine had faecal stasis proximal to active colitis which went into remission with hydrophilic colloid therapy and unchanged SASP therapy. In the group in remission (43), 23% had faecal stasis.

This suggests that SASP or its metabolites SP or 5 amino-salicylic acid act topically in the colon and that serum SP concentrations are secondary correlations.

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#### Effect of low dose steroids on clinical relapse in Crohn's disease

J. RHODES, R. M. SMITH, L. E. HUGHES, D. L. CROSBY, B. REES, H. JONES, R. V. HEATLEY, K. T. EVANS, AND B. W. LAWRIE (University Hospital of Wales, Heath Park, Cardiff) The effect of low dose steroids (7.5 mg prednisone daily in adults and on alternate days in patients less than 14 years old) has been examined in a double-blind controlled trial in 64 patients who did not appear to need steroids. Twenty-six (group I) had recently had all apparent disease removed by surgery; 11 (group II) were known to have residual disease after surgical resection, and 22 (group III) had not undergone surgical resection. Five patients were withdrawn within six months for reasons other than clinical relapse. Thirty-three of the patients received

steroids and 26 placebo therapy for between six months to three years; 30 patients have been in the trial for three years. A clinical relapse was defined at the onset of the trial and occurred when additional steroids had to be given (four patients), or if surgery were necessary (10 patients); patients who required steroids for more than six weeks were withdrawn from the trial. Eight of the 14 patients withdrawn were on active therapy and six on placebo. The overall relapse rate at three years was 30%.

Prednisone, 7.5 mg daily, does not appear to reduce the risk of recurrent disease or clinical relapse in patients with Crohn's disease who at the onset of the trial did not require steroids.

#### National Cooperative Crohn's Disease Study (NCCDS): a controlled prospective trial of three drugs vs placebo

R. W. SUMMERS (University Hospitals, Iowa City, Iowa, introduced by D. L. WINGATE) and J. W. SINGLETON (Coordinating Center: GI Division, University of Colorado Medical Center, Denver) The NCCDS randomised 584 patients at 14 centres in a double-blind comparison of prednisone-P, sulfasalazine-S, azathioprine-A, with a placebo control-C. Response was analysed using the Wilcoxon Rank Sum method and a Crohn's Disease Activity Index (CDAI), an eight-item numerical clinical index of degree of illness<sup>1</sup>. In Part I, phase 1, 300 patients with active symptomatic disease (CDAI 150) were followed for 17 weeks. Response to P or S was better than to C (P = 0.001, P = 0.017). Response to A did not differ from C (P = 0.32). In patients on steroids at randomisation (n = 51), substitution of S was no better than substitution of C (P = 0.94); however, continuation of steroids on P was superior to C (P = 0.025). Separate comparison of coded initial and final barium x-rays showed improvement with P, but not with S, A, or C. In Part I, phase 2 the 95 patients responding favourably to phase 1 therapy (CDAI 150 at week 17) were followed to see whether continued drug therapy at reduced dose would maintain remission. Response to any drug was no different from that to C at either one or two years. In Part II, a prophylactic effect of low dose therapy against flare-up or recurrence was sought in 284 patients who had either quiescent disease (CDAI 150), or who had surgical resection of all involved bowel within a year before entry. Response to any drug

was no different from that to C at either one or two years. Clinical or x-ray deterioration had occurred in 32% at one year and 69% in two years.

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#### Electrolyte depletion in patients with ileostomies: a failure of normal homeostasis?

A. I. MORRIS, P. C. HAWKER, AND L. A. TURNBERG (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford. Horth, C. E. Biochemical Pharmacology Department, G. D. Searle and Co. Ltd., High Wycombe) Clarke and his colleagues<sup>1</sup> have suggested that patients with established ileostomies are chronically dehydrated and salt depleted. We have investigated the extent of electrolyte depletion, assessed possible mechanisms for it and searched for adaptive hormonal responses in 14 ileostomists.

Using an isotope dilution technique (Skrabal *et al.*<sup>2</sup>) nine women and one of five men with established ileostomies were shown to have a significantly reduced total exchangeable sodium. All the women and three men were strikingly potassium depleted, a finding not previously demonstrated. No patient had significantly reduced total body water or ECF volumes.

There was no evidence of renal retention of sodium or potassium in the face of depletion and there was no correlation between total exchangeable sodium or potassium and daily urinary or ileostomy losses of sodium, potassium or water.

Plasma aldosterone concentrations were normal in all but one patient, as were plasma renin and prolactin concentrations.

We conclude that apparently healthy ileostomists are usually significantly potassium depleted, commonly sodium depleted, but not dehydrated. They appear to have adjusted to a new state of stable but depleted electrolyte balance without a maintained change in plasma salt retaining hormone concentrations and without evidence of renal or intestinal sodium and potassium conservation.

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aneous electrolyte investigations in man using <sup>71</sup>Br, <sup>42</sup>K and <sup>24</sup>Na. *International Journal of Applied Radiation and Isotopes*, 21, 183-191.

#### Controlled comparison of sodium cromoglycate and sulphasalazine in the maintenance of remission in ulcerative colitis

M. W. DRONFIELD AND M. J. S. LANGMAN (Department of Therapeutics, City Hospital, Nottingham) The results of preliminary trials have suggested that sodium cromoglycate (SCG) may be effective in the treatment of active ulcerative proctocolitis<sup>1,2</sup>, and bearing in mind the prophylactic role of SCG in bronchial asthma, we are comparing it with sulphasalazine (SSZ) in patients with ulcerative colitis in remission.

Twenty-four patients have so far been randomly allocated to SSZ treatment 2 g/day, 17 to high dose SCG (2 g/day) and 12 to low dose SCG (160 mg/day). The cumulative proportion of patients free of relapse after six months of treatment is 0.71 in the SSZ treated group, 0.58 in the high dose SCG group, and 0.29 in the low dose SCG group. One patient could not tolerate high dose SCG because it produced intolerable urgency of defaecation, but no other withdrawals because of side-effects have been necessary, and no haematological or biochemical abnormalities have been found.

These preliminary results show that low dose SCG is relatively ineffective, but that results with high dose SCG are intermediate between those with the low dose and SSZ. If current trends are maintained SCG in a dose of 2 g/day could prove a useful second drug for maintaining remission in ulcerative colitis.

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#### OESOPHAGUS

#### Pattern of nocturnal gastro-oesophageal reflux

R. J. R. GOODALL, D. J. HAY, D. W. WARD, AND J. G. TEMPLE (Introduced by M. H. IRVING) (Department of Surgery, Hope Hospital (University of Manchester School of Medicine), Salford, Lancs., and Gastroenterology Unit, Broadgreen Hospital,

Liverpool) It is commonly held that gastro-oesophageal reflux occurs more frequently during sleep<sup>1,2</sup>. At this time its effects are said to be more dangerous, as the influence of gravity is reduced and swallowing is less frequent. We cannot confirm this pattern of prolonged nocturnal reflux and, in addition, have noticed that, if reflux occurs during sleep, swallowing occurs normally.

Continuous overnight pH measurements have been recorded from a position 5 cm above the gastro-oesophageal sphincter in 24 patients and seven controls. The patients had symptomatic oesophagitis confirmed by endoscopy or radiology. None had oesophageal stricture or gastro-duodenal ulceration. Reflux was judged to have occurred when the pH fell below 4.

In the control group the mean duration of reflux between 6.00 pm and 12.00 pm was 56.4 minutes  $\pm$  SEM 17.4 and between 12.00 pm and 6.00 am 11.4 minutes  $\pm$  8.2 ( $P = < 0.05$ ). In the patients, the duration of reflux was 71.5 minutes  $\pm$  14.5 and 24.3 minutes  $\pm$  9.2 respectively ( $P = < 0.01$ ). There was, however, no significant difference between the two groups themselves.

Further analysis shows that reflux activity reflects the patients' activity, in that it falls as the patients go to sleep and rises again after 6.00 am. This was also the pattern in the control subjects.

In view of these findings we feel that nocturnal supine reflux may not be very important in patients with oesophagitis.

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#### Transmucosal potential difference; diagnostic value in gastro-oesophageal reflux

B. KHAMIS, C. KENNEDY, J. FINUCANE, AND J. STEPHEN DOYLE (Department of Gastroenterology, St. Laurence's Hospital, Dublin) It has been suggested that transmucosal potential difference (PD) reflects the mucosal integrity<sup>1</sup> and that any disruption of the mucosa causes a fall in PD.

In this study we have measured PD in 19 patients in the lower oesophagus. The exploring electrode was firmly placed against the mucosa, 5 cm above the gastro-oesophageal mucosal junction under direct vision via an endoscope and



biopsy specimens were subsequently obtained from the same site.

The histological criteria for diagnosis of gastro-oesophageal reflux were those laid down by Ismail-Beigi and his colleagues<sup>2</sup>.

In 10 patients with normal biopsy specimens, the mucosal surface was always electro-negative with respect to the body surface (mean  $-14.4 \text{ mV} \pm 0.4 \text{ mV SEM}$ ). In nine patients with histological changes of gastro-oesophageal reflux mean value was  $+9.4 \text{ mV} (\pm 3.0 \text{ mV SEM})$  a reversal of polarity in all but one case.

Excellent correlation was also found between histological findings, PD, and symptoms of lower oesophageal disease such as heartburn, lower retrosternal pain, and dysphagia. Visual appearance was a less reliable predictor of reflux changes.

Measurement of PD provides a simple, rapid and reliable index of lower oesophageal mucosal integrity and may prove useful in diagnosis and assessment of therapy.

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#### Gastro-oesophageal reflux in duodenal ulcer and after parietal cell vagotomy (PCV), selective gastric vagotomy plus drainage (SGV + D) and selective gastric vagotomy plus antrectomy (SGV + A)

M. ØSTER, A. CSENDES, O. BRANDSBORG, M. BRANDSBORG, AND E. AMDRUP (*Surgical Gastroenterological Department L, Kommunehospitalet, University of Århus, Denmark*) Gastro-oesophageal reflux was determined by intraoesophageal pH measurement in 20 patients with duodenal ulcer, 15 patients after PCV, 15 patients after SGV + D, and 12 patients after SGV + A. The average time between the operation and this study was 30 months (range 12 to 50). Gastro-oesophageal sphincter pressure (GOSP) and the response of GOS to graduated increase in intra-abdominal pressure were determined in each case. Duodenal ulcer patients had reflux symptoms in 45% of the cases and the majority of these had a positive acid reflux test. No correlation between serum gastrin concentrations and resting GOSP was found. The increase in sphincter pressure with abdominal com-

pression was similar before and after surgery. The incidence of reflux symptoms were similar to nonoperated duodenal ulcer patients in patients submitted to PCV or SGV + D, but higher in patients after SGV + A. Gastro-oesophageal reflux measured by oesophageal pH was present in similar proportion of patients after surgery.

**Conclusion** (1) Reflux oesophagitis symptoms and gastro-oesophageal reflux are present in an important percentage of nonoperated duodenal ulcer patients. (2) The severity of reflux symptoms in patients with PCV or SGV + D were similar to nonoperated cases. In patients with an associated antrectomy, symptoms and gastro-oesophageal reflux were more pronounced.

#### Effect of extrinsic denervation of the lower end of the oesophagus on resting and cholinergic-stimulated gastro-oesophageal sphincter pressure

A. CSENDES, M. ØSTER, J. MØLLER, O. BRANDSBORG, M. BRANDSBORG, AND E. AMDRUP (*Surgical Gastroenterological Department L, Kommunehospitalet, University of Århus, Denmark*) Twelve patients with duodenal ulcer were studied one week before and one week and 12 weeks after randomised surgery. Seven patients were submitted to parietal cell vagotomy (PCV) and five patients to selective gastric vagotomy (SGV + D). Resting gastro-oesophageal sphincter pressure (GOSP) and serum gastrin concentrations were measured. The response of the GOS to 2 or 4  $\mu\text{g/kg}$  body weight of carbacholine was measured every 10 minutes for 90 minutes after the subcutaneous injection.

There was no significant change in resting GOSP after PCV or SGV + D. The response of GOSP to the cholinergic drug was dose dependent before and after surgery. In all patients a depressed response to carbacholine was observed one week after surgery, which was restored to normal preoperative values 12 weeks after surgery. Three patients had a transient low dysphagia starting one week after surgery and disappearing in two months. Sphincter relaxation reached fundic pressure in all patients. Resting intraoesophageal pressure was always negative and no change in the amplitude of the peristaltic waves of the distal oesophagus was recorded. Basal serum gastrin concentrations were higher after surgery in every case.

**Conclusion** (1) No significant changes of the GOSP were recorded after extrinsic denervation of the lower end of the oesophagus. (2) No manometric features of achalasia were seen in any case, in spite of the presence of dysphagia in three cases. (3) Postoperative transient dysphagia is mainly due to mechanical factors and not to denervation of the lower oesophagus and 'transient achalasia'.

#### Cricopharyngeal myopathy and fibrosis

P. CRUSE, D. A. W. EDWARDS, J. F. SMITH, AND J. H. WYLLIE (*Departments of Pathology and Surgery, University College Hospital Medical School, London*) Cricopharyngeal 'achalasia' causing dysphagia is usually attributed to neuromuscular incoordination and a specific histological change in the muscle has not been clearly described.

Cricopharyngeus muscle from 20 necropsies on patients without dysphagia; biopsies from seven patients with cricopharyngeal 'achalasia', from three patients with pharyngeal pouch, and from one patient with motor neurone disease were examined by light microscopy.

Tissue from patients with cricopharyngeal 'achalasia' showed damage to muscle fibres (shrinkage, internal nuclei, nuclear condensation, phagocytosis) and increased intermuscular stroma which looked like fibrous tissue and stained like collagen. Nerves seen were normal. Fibrosis was *not* noted in controls, patients with pouch, or motor neurone disease, nor in adjacent muscles from two patients with fibrosis, nor in any of the 14 pharyngeal and laryngeal muscles examined post mortem from another patient with cricopharyngeal fibrosis.

It seems likely that the histological features of cricopharyngeal 'achalasia' are specific, the disorder is localised to the cricopharyngeus and the dysphagia is caused by the resistance to stretch of the fibrous tissue rather than by a disorder of timing of contraction and relaxation of the muscle. Myotomy can produce dramatic relief of dysphagia.

#### Dysphagia in Parkinson's disease—a study of oesophageal motility and vagal function

M. G. BRAMBLE, J. CUNLIFFE, AND A. W. DELLIPIANI (*North Tees General Hospital, Hardwick, Stockton*) To investigate a possible disease specific disturbance of oesophageal motility as a cause of dysphagia in Parkinson's disease (PD)

oesophageal manometry was performed in 20 affected patients and 20 controls, matched for age and sex. The recording system incorporated a triple lumen tube perfused at 0.6 ml/min, Statham transducers, and a Devices recorder. Vagal function was assessed by measuring resting R-R interval on an ECG and beat to beat variation of the same on deep breathing<sup>1</sup>.

Recordings were repeated after bethanechol (17 patients) and atropine (15 patients).

No differences emerged between the two groups in respect of all the parameters measured on the basal recordings. After bethanechol, aperistalsis significantly increased in the PD group ( $p=0.02$ ), though comparison with controls failed to achieve significance. Atropine increased the percentage of aperistaltic swallows in both groups ( $p=0.001$ ), though this was significantly greater in the PD group ( $p=0.05$ ).

A relationship between dysphagia, severity of disease, and evidence of an autonomic neuropathy was explained by age alone. Beat to beat variation diminished with increasing age in the PD group ( $r = -0.580$ ,  $p=0.01$ ) and controls ( $r = -0.468$ ,  $p=0.05$ ).

Increased sensitivity to atropine may be due to a disease specific change in neurotransmitter in the dorsal vagal nucleus<sup>2</sup>, but does this produce intermittent dysphagia?

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#### Effects of two types of pylorus preserving operations on lower oesophageal sphincter pressure (LOSP) and the correlation with endogenous gastrin levels

P. V. DELANEY, P. J. BYRNE, AND T. P. J. HENNESSY (*Trinity College, Department of Surgery, Sir Patrick Dun's Hospital, Dublin*) There are conflicting reports on the influence of gastrin on the lower oesophageal sphincter in man. The relevance of these reports is doubtful because the gastrin levels achieved are mostly pharmacological<sup>1</sup>. Pylorus preserving gastrectomy (PPG) causes a significant reduction in gastrin levels<sup>2</sup>, whereas highly selective vagotomy (HSV) produces the reverse effect<sup>3</sup>. These patients provide an

ideal opportunity to study the effects of gastrin under physiological conditions.

Two groups of eight patients were studied after PPG and HSV to determine the effects on LOSP of (1) physiological variations of endogenous gastrin, and (2) two types of pylorus preserving operation.

LOSP was measured and blood taken for gastrin assay—fasting and at one and two hours after a standard protein meal. Pressures were recorded on a Mingograph multiple channel recorder *via* side hole constantly perfused cannulas.

Results showed that gastrin levels were significantly higher after HSV ( $p < 0.01$ ; one tailed *t* tests); there was no significant difference between LOSPs in the two groups ( $p > 0.1$ ; one tailed *t* tests); there was no significant correlation between gastrin levels and LOSP (Pearson's  $r < 0.2$ ;  $p > 0.2$ ).

**Conclusions** LOSP in man is not significantly affected by physiological variations in gastrin concentration; HSV or PPG does not affect the LOSP mechanism.

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#### Effect of coffee on human lower oesophageal function

S. S. FEDAIL, P. R. SALMON, H. P. WURZNER, R. F. HARVEY, AND A. E. READ (*University Department of Medicine, Bristol Royal Infirmary, Bristol*) The physiological effect of coffee and caffeine on the oesophagus has been the subject of a number of studies<sup>1,2</sup>; the results, however, have been conflicting. Lower oesophageal sphincter pressure (LOSP) using the rapid pull-through technique<sup>3</sup>, and intraoesophageal pH using an indwelling micro-electrode were measured in healthy volunteers under different conditions.

Each subject was studied five times both fasting and after a standard meal. The effect of standardised coffee, black and with milk, was assessed by sequential LOSP measurements. Intraoesophageal pH was continuously monitored basally and in response to standard acid reflux tests.

Coffee with or without milk has no significant effect on LOSP in the fasting sub-

ject. The standard meal alone dropped LOSP significantly from a basal value (mean  $\pm$  SEM) of  $12.64 \pm 1.24$  cm of  $H_2O$  to  $10.63 \pm 1.57$  cm of  $H_2O$  ( $t = 2.437$ ,  $p < 0.05$ ). Coffee with milk after the meal also dropped LOSP from  $13.83 \pm 2.08$  cm of  $H_2O$  to  $12.03 \pm 1.79$  cm of  $H_2O$  ( $t = 2.375$ ,  $p < 0.05$ ). Black coffee after the meal produced no significant change in LOSP. A significant acid reflux was found in two non-fasting subjects after coffee.

These results suggest that black coffee might prevent the postprandial drop in LOSP.

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#### Significance of measurements of lower oesophageal sphincter pressure in patients with symptomatic gastro-oesophageal reflux

M. G. GREANEY, D. K. CHATTOPADHYAY, AND T. T. IRVIN (*University Surgical Unit, Royal Infirmary, Sheffield*) It is alleged that weakness of the lower oesophageal sphincter is a significant factor in the pathogenesis of gastro-oesophageal reflux<sup>1</sup>, but manometric studies of lower oesophageal sphincter pressure (LOSP) have failed to demonstrate any consistent abnormality in symptomatic patients. These findings may be due to the variables which affect the fidelity of LOSP measurements, and it has been suggested that more accurate measurements of LOSP are achieved with a new rapid pull-through (RPT) technique of manometry<sup>2</sup>.

LOSP measurements were made in 30 asymptomatic volunteers (group 1) and in 27 patients with symptomatic gastro-oesophageal reflux (group 2) using the RPT method of manometry. Basal LOSP measurements were made and the effects of abdominal compression and intravenous metoclopramide (10 mg) on LOSP were determined. There was no significant difference in basal LOSP measurements in the two groups, and intravenous metoclopramide was followed by a similar increase in LOSP in both groups ( $25.4 \pm 7.0\%$  in group 1, and  $23.2 \pm 7.6\%$  in

group 2). Abdominal compression caused a rather greater increase in LOSP in group 2 ( $50.5 \pm 15.8\%$ ) compared with group 1 ( $27.1 \pm 11.9\%$ ) but the difference is not statistically significant.

The results suggest that RPT measurements of LOSP do not distinguish between normal subjects and patients with symptomatic reflux.

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#### Variation in resting lower oesophageal sphincter tone: a neglected factor affecting recording accuracy?

D. J. HAY, R. J. R. GOODALL, AND J. G. TEMPLE (introduced by M. H. IRVING) (*Department of Surgery, Hope Hospital (University of Manchester School of Medicine), Salford*) Using a multi-lumen catheter assembly for the measurement of lower oesophageal sphincter pressure (LOSP) by the station pullthrough technique (SPT), spurious between channel pressure variation is common. Radial pressure asymmetry is said to be responsible for this<sup>1</sup>.

SPT was performed twice upon the same day on 10 normal subjects, each test after a fast of at least four hours. In one test, a water perfused tube with three radially orientated orifices situated 5 cm from the tip (tube I) was used, and in the other test the orifices were similarly arranged, but at 15 cm (tube II). The tests were carried out in random order.

Resting LOSP was calculated as the mean of the three pressure channel recordings. Using tube I the mean LOSP was  $9.88 \text{ mm Hg} \pm \text{SD } 3.81$ , whereas with tube II it was  $14.1 \text{ mm Hg} \pm \text{SD } 5.03$ , this difference being significant ( $P < 0.001$ ). The highest and lowest pressure channel recordings in each test were also compared and showed a significant variation ( $P < 0.001$ ).

These results confirm that radial pressure asymmetry is a cause of variation in resting lower oesophageal sphincter pressure measurement, but equally important in recording accuracy appears to be the length of catheter assembly which projects into the gastric lumen below the recording orifices.

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#### LIVER AND BILIARY II

#### Clinical pharmacology of oral chenodeoxycholic acid (CDCA)

M. PONZ DE LEON AND R. HERMON DOWLING (*Guy's Hospital and Medical School, London*) For many drugs, efficacy relates to peripheral blood concentration and bioavailability to areas under 'tolerance' (concentration-time) curves—AUCs. However, CDCA's effect in dissolving gallstones is within the liver and peripheral levels represent only hepatic 'spillover'. To study CDCA bioavailability, therefore, in nine control subjects we measured (1) solubility of 500 mg oral CDCA (gelatin-coated capsules) in aspirated intestinal contents, (2) CDCA absorption from aqueous intraduodenal solutions (250, 500, and 750 mg) of <sup>3</sup>H-CDCA containing nonabsorbable marker <sup>14</sup>C-PEG, (3) resultant four hour serum CDCA tolerance curves, and (4) corresponding AUCs after 250, 500, and 750 mg CDCA in capsules given (a) during fasting, (b) with food.

Results showed that (1) the distribution ratio (aqueous phase : precipitate) of ingested CDCA in ultracentrifuged intestinal contents ranged from 1:49 at pH 2.9 (stomach) to 9:1 at pH 6.7-7.5 (jejunum); however, CDCA 'solubility' seemed independent of endogenous conjugated bile salts at concentrations  $> 2.3 \text{ mM}$ ; (2) CDCA 'absorption', as judged by <sup>3</sup>H:<sup>14</sup>C ratios, was 96-100% complete after 0.5-1 h, 120 cm distal to duodenal infusion site; (3) absolute AUCs increased with increase in capsule and infusion CDCA dose but percent of dose spilling into peripheral blood diminished with increasing numbers of capsules; (4) comparing AUCs and using duodenal infusion for reference, CDCA absorption (250 and 500 mg in capsules) was 100% complete.

**Summary** Ingested CDCA is solubilised with increasing intestinal pH, appears well absorbed, and seems to be highly 'bioavailable'.

#### Efficacy of withdrawal from and resistance to chenodeoxycholic acid treatment in patients with gallstones

P. N. MATON, J. H. ISER, G. M. MURPHY, AND R. HERMON DOWLING (*Guy's Hospital and*

*Medical School, London*) Efficacy Of 135 gallstone patients accepted for treatment 116 have radiolucent stones and a functioning gallbladder, in those 40 with stones  $< 15 \text{ mm}$  diameter treated for one year with  $\geq 13 \text{ mg kgBw}^{-1} \text{ day}^{-1}$  and who achieved unsaturated bile, efficacy reached 65% (complete gallstone dissolution) or 93% (partial + complete). **Withdrawal** Of 44 patients stopping CDCA (27 surgery) nine defaulted  $< 1$  month, 14 stopped  $< 1$  year, two died (unrelated causes), seven had  $> 15 \text{ mm}$  stones, seven took  $< 13 \text{ mg kgBw}^{-1} \text{ day}^{-1}$ , three had noncholesterol stones or debris, one took clofibrate (which causes supersaturated bile<sup>1</sup>), six developed non-opacifying gallbladders, and four biliary colic  $\pm$  pancreatitis. Thus few patients stopped treatment because of CDCA failure *per se*.

**Resistance** Failure to achieve unsaturated bile despite  $13\text{-}15 \text{ mg kgBw}^{-1} \text{ day}^{-1}$  occurred in 19 patients, including eight obese patients who ultimately achieved unsaturated bile with increased dosage ( $18.6 \pm 1.4 \text{ mg CDCA/kg}$ )<sup>2</sup>. Two obese and four non-obese patients had supersaturated bile despite  $19\text{-}22 \text{ mg CDCA/kg}$  and  $> 70\%$  CDCA in biliary bile acids (suggesting compliance). The mechanism of CDCA 'resistance' in these patients is unknown but results on one patient suggest excess hepatic cholesterogenesis (HMGC<sub>o</sub>A reductase activity  $143 \text{ pmol microsomal protein mg}^{-1} \text{ min}^{-1}$ ; untreated gallstone patients 65-76).

**Summary** Despite the high withdrawal rate, in selected patients CDCA is effective and treatment failure infrequent. A new syndrome of resistance to CDCA has been identified.

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#### Dissolution of radiolucent gallstones using a fixed dose of chenodeoxycholic acid

M. C. BATESON, P. E. ROSS, J. MURISON, AND I. A. D. BOUCHIER (*Department of Medicine, Ninewells Hospital and Medical School, Dundee*) The ideal dose of chenodeoxycholic acid in the treatment of radiolucent gallstones has yet to be established and there is much disagreement



in the literature. We report our experience with 750 mg/day chenodeoxycholic acid in 48 patients with gallbladder stones, of whom 38 have been followed for six to 36 months. Complete dissolution was achieved in six and partial dissolution in five patients. In contrast with previous reports, response did not depend upon dosage/unit body weight nor on gallstone size. The composition of fasting bile showed a drop in the percent of cholesterol and a rise in bile acids but values did not become normal even in patients with successful dissolution. Biliary symptoms improved even in the absence of dissolution. No important changes were observed in serum biochemistry or the histology of stomach, jejunum, and liver. After dissolution patients were maintained on 500 mg/day and stones recurred in two of four patients reviewed at 12 months. The use of 1000 mg/day in 22 patients failing to respond to 750 mg daily was accompanied by unacceptable diarrhoea in eight. One of nine patients with common bile duct stones achieved dissolution on 750 mg/day and there was a high proportion of unacceptable side effects. We make recommendations for the use of chenodeoxycholic acid based on this experience.

#### Rowachol—a possible treatment for cholesterol gallstones?

J. DORAN, M. R. B. KEIGHLEY, AND G. D. BELL (*University Department of Therapeutics, City Hospital, Nottingham and General Hospital, Birmingham*) The proprietary terpene preparation Rowachol (R)\* has been marketed extensively on the Continent as a choleric for over 25 years. In the rat it significantly reduces biliary cholesterol secretion<sup>1</sup>. In man, there have been a number of case reports of gallstones dissolving during R treatment<sup>2</sup>. The present study examines the effect of R on biliary lipid composition.

Gall bladder bile was obtained at cholecystectomy from 30 patients with gallstones and functioning gall bladders. Eighteen patients received R preoperatively at a dose of either 1 or 2 capsules tds for 48 hours, while the remaining 12 acted as controls. The cholesterol saturation index<sup>3</sup> (CSI  $\pm$  SD) in the control subjects ( $1.46 \pm 0.40$ ) was similar to that of the patients given the smaller R dose ( $1.38 \pm 0.09$ ). However, at the higher dose R significantly ( $P < 0.001$ ) lowered the CSI ( $0.88 \pm 0.15$ ). The biliary cholesterol secretion in eight patients with a T-tube *in situ* given R in a dose of three capsules tds

for 72 hours was less than that of 10 control patients, and as a result the CSI was again significantly ( $P < 0.01$ ) lowered by the drug.

**Conclusion** R may prove an effective alternative to chenodeoxycholic acid in the treatment of patients with cholesterol gallstones.

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- \*Rowa Ltd., Bantree, Co. Cork, Eire.

#### Local infusion therapy for radiolucent retained common duct stones using sodium cholate, heparinised saline, and physiological saline

M. C. BATESON AND I. A. D. BOUCHIER (*Department of Medicine, Ninewells Hospital and Medical School, Dundee*) Twenty patients have been referred over 2½ years for non-operative treatment of retained radiolucent gallstones.

One had a hepatic duct stone which disappeared on removal of the T-tube. All others started on a regime of infusion therapy with sodium cholate, or heparinised saline or physiological saline.

Twelve patients received sodium cholate 100 mM initially. There were five successful treatments, three after five and two after 10 days. In five patients toxicity limited therapy, and in three of those reviewed at five days stones persisted.

Five patients received heparinised physiological saline (100 000 units/l) for 10 days. There were two successes and three failures. The failures proceeded to sodium cholate infusion for 10 days without success.

Of two patients treated with physiological saline alone, one showed resolution of stones at 10 days.

Therefore altogether 15 patients received sodium cholate with five successes, and seven patients received heparinised or physiological saline with three successes without serious side-effects.

All saline infusions used removed common bile duct stones, but sodium cholate is associated with frequent severe side-effects. Whether sodium cholate resolves stones resistant to infusion of other

fluids remains to be determined, and its current place in therapy is under review.

#### Epidemiological study of neonatal hepatitis syndrome in infancy: incidence and early course

A. P. MOWAT, H. PSACHAROPOULOS, AND R. WILLIAMS (*King's College Hospital Medical School, London*) From January 1971 to December 1973, all infants developing the hepatitis syndrome within a circumscribed area (population 3.5 million) were prospectively investigated to determine the incidence of known causes and are regularly reviewed to assess factors of prognostic significance. Fifty-four cases were identified from 137 000 live births. Eleven had extrahepatic biliary atresia, seven dying in the first year of life, two in the second. The two current survivors have cirrhosis, are frequently jaundiced and have bled from varices. Four of seven infants with the genetic deficiency of alpha-1-antitrypsin died with cirrhosis by 3 years of age. Two survivors are clinically well but have raised serum transaminases; the third has cirrhosis. All three infants with confirmed congenital infection and one infant with trisomy 18 died in the first year of life with severe cardiac and central nervous system abnormalities.

Twenty-nine infants had cryptogenic hepatitis. Two died at eight and 12 weeks after laparotomy. Jaundice cleared in the remainder in two to 36 weeks. At 1 year of age, 11 had raised transaminases, one having hepatosplenomegaly, and three splenomegaly. A further two children had hepatomegaly. At recent follow-up (mean age 4.9 years), only four children had any evidence of liver disease, one having cirrhosis and three mild persistent hepatitis. Cryptogenic hepatitis is thus approximately three times as common as biliary atresia or hepatitis with alpha-1-antitrypsin deficiency and has a much better prognosis than suggested by previous reports<sup>1,2,3</sup>.

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**Prognosis in childhood of liver disease associated with alpha-1-antitrypsin deficiency, type PiZ (Alpha-1-antitrypsin deficiency)**

A. P. MOWAT, H., PSACHAROPOULOS, R. WILLIAMS, B. PORTMAN, AND R. A. J. TAIT (*King's College Hospital Medical School, London*) Prospectively recorded data in 33 children with alpha-1-antitrypsin deficiency in liver disease were analysed to determine the course and features of prognostic importance. In 32 acute hepatitis developed in the first four months of life. Serum bilirubin fell to normal in four to 48 weeks, but serum transaminase and alkaline phosphatase remained abnormal, except in seven children (group 1) who are now well aged 2-9 years (mean 5.1). Eighteen survive with persistently abnormal liver function tests, eight having cirrhosis (group 2, age 1-10 years, mean 5.0), eight died of cirrhosis (group 3, age 1-8 years, mean 5.3).

The prognosis in these groups was related to the severity of the acute hepatitis, jaundice lasting 11, 14, and 20 weeks and the mean maximum AST concentration 88, 173, and 295 IU/litre in groups 1, 2, and 3 respectively. Semi-quantitative assessment of liver biopsies in the first six months of life showed in group 1 much more prominent hepatocellular infiltration, and much less portal tract fibrosis and bile duct proliferation than in groups 2 and 3. Four already had cirrhosis, including one who had a clinically mild hepatitis.

Combined clinical, biochemical, and histological assessment is necessary to assess prognosis of liver disease in alpha-1-antitrypsin deficiency.

**Effect of bovine pancreatic polypeptide (BPP) infusions on gastric and biliary function in man**

G. R. GREENBERG, R. F. MCCLOY, V. S. CHADWICK, T. E. ADRIAN, J. H. BARON, AND S. R. BLOOM (*Royal Postgraduate Medical School, Hammersmith Hospital, Duane Road, London*) The role of pancreatic polypeptide in human physiology is unknown yet plasma concentrations rise rapidly after a meal. Because powerful biological effects in gastric and biliary function are reported for the dog, we investigated these parameters in man. Using simultaneous gastric and duodenal perfusion techniques to measure basal gastric and biliary outputs, six healthy subjects received IV infusions of BPP to

achieve plasma levels comparable with those observed post-prandially. In separate experiments (N = 8) the effect of BPP on stimulated gastric secretion was assessed by infusing pentagastrin at 0.7 µg/kg-h to achieve 50% MAO.

Mean basal and stimulated gastric acid outputs of 3.5 ± 0.8 (mmol/h) and 25.0 ± 4.5 (mmol/h) respectively were unaffected by BPP infusion as was pepsin secretion. However, under basal conditions BPP decreased mean net intraduodenal fluid accumulation by 76 ± SEM 4.7%. This was associated with a highly significant reduction (>90%) in bilirubin output with a variable period of recovery in the post-infusion hour.

We conclude that BPP infusions in man which achieve physiological plasma concentrations (1) have no effect on basal or pentagastrin-stimulated acid or pepsin secretion; (2) reduce bilirubin output suggesting a possible role in the regulation of gallbladder storage.

**Relative value of lymphocyte cytotoxicity for hepatocytes and conventional blood tests in assessment of histological activity in chronic active hepatitis**

A. M. G. COCHRANE, B. PORTMANN, A. L. W. F. EDDLESTON, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London*) Management of immunosuppressive therapy in patients with chronic active hepatitis, in the absence of repeated liver biopsies, is dependent on changes in standard liver function tests. We have assessed the value of these tests in predicting histological activity, and have compared them with the results of a test of specific autoimmune reactivity, lymphocyte cytotoxicity for isolated hepatocytes. Histological activity was determined subjectively, and individual features scored to give a quantitative index. Patients with an active biopsy had significantly higher levels of aspartate aminotransferase, bilirubin, alkaline phosphatase, IgG, and cytotoxicity, than those with an inactive biopsy. There was also a significant quantitative relationship between these same indices and the biopsy score.

However, when the chi-squared test was used to assess the value of a normal or abnormal test result in predicting disease activity, only two of the tests led to significant differentiation—total globulin. (P < 0.05) and lymphocyte cytotoxicity for isolated hepatocytes (P < 0.0005).

These results suggest that conventional blood tests are unreliable in assaying

histological activity and unsuitable parameters for determining changes in immunosuppressive drug doses. Although the cytotoxicity assay is too cumbersome for routine use, the results indicate the potential importance of tests of specific immunological reactivity in the management of chronic active hepatitis.

**Radioimmunoassay for antibodies to human liver-specific membrane lipoprotein (LSP) in chronic active hepatitis and chronic persistent hepatitis**

D. JENSEN, I. G. MCFARLANE, A. L. W. F. EDDLESTON, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London*) Indirect evidence suggests that antibody to a liver membrane lipoprotein (LSP) in co-operation with K-cells plays a pathogenetic role in the continuing hepatocellular necrosis in chronic active hepatitis (CAH). Using highly purified LSP labelled with <sup>125</sup>I, we have developed a solid phase radioimmunoassay for detection of anti-LSP antibodies in serum. The specificity of the assay has been demonstrated by blocking experiments with LSP, other liver proteins, F-actin, and plasma proteins.

Circulating anti-LSP was found in all of nine patients with HBsAg-negative CAH and in eight of nine with HBsAg-positive CAH. Titres ranged from 1:200 to 1:2400 (log mean 1:550) and were similar in both groups. Eight of 13 patients with chronic persistent hepatitis (CPH) also had anti-LSP, but at significantly lower titres (P < 0.01) ranging from 1:50 to 1:400 (log mean 1:120), with no significant difference between HBsAg-positive and negative cases. Anti-LSP was not found in the sera of a control group of nine patients with idiopathic haemochromatosis.

This sensitive and reproducible radioimmunoassay provides direct evidence of the presence of antibody to LSP in chronic active hepatitis. The finding of lower titres in chronic persistent hepatitis suggests that levels of the antibody may be related to severity of liver damage.

**DNA binding antibodies in HBsAg positive and negative acute and chronic liver disease**

J. G. C. KINGHAM, N. K. GANGULY, S. T. HOLGATE, D. R. TRIGER, M. MCGUIRE, B. COHEN, S. RASSAM, AND RALPH WRIGHT (*Professorial Medical Unit, Southampton General Hospital, Southampton*) High double-stranded DNA binding antibodies were initially thought to be specific for

systemic lupus erythematosus but subsequently were reported in chronic active hepatitis<sup>1,2</sup>. The findings in other forms of liver disease have been conflicting, with considerable overlap with the normal range<sup>1,2</sup>.

Using a modified Farr technique, we have found high DNA binding in a wide range of acute and chronic liver diseases in United Kingdom patients with acute hepatitis (21), HBsAg negative chronic active hepatitis (38), primary biliary cirrhosis (18), cirrhosis (17), and alcoholic liver disease (15) with little overlap with healthy controls. Forty-seven patients with HBsAg positive liver disease from Iraq had significantly higher DNA binding levels ( $21.8 \pm 3.7\%$ ) than 46 who had no hepatitis B markers ( $13.3 \pm 2.9\%$ ). Six HBsAg-negative but HB core antibody positive patients formed an intermediate group. Hepatitis B associated groups were well above 48 controls ( $7.5 \pm 1.7\%$ ).

High DNA binding antibodies in liver disease may be due to release of hepatic nuclear DNA, macrophage sequestered exogenous DNA or specific viral DNA.

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#### Peripheral macrophage function in patients with chronic liver disease

D. R. TRIGER, J. G. C. KINGHAM, R. S. LLOYD, AND RALPH WRIGHT (*Department of Medicine, Southampton University, Southampton*) One of the mechanisms postulated to account for the hyperglobulinaemia in chronic liver disease is an inability of the liver to sequester antigens because of a defect in liver macrophage function. Because of the difficulty in isolating Kupffer cells, an attempt to assess macrophage function in man has been made by isolating macrophages from the peripheral circulation and examining their functional properties. Twenty-seven patients with chronic liver disease (12 alcoholic and 15 non-alcoholic) were studied and the results compared with those obtained from simultaneously studied age/sex matched healthy controls. Macrophage preparations were obtained by differential centrifugation of heparinised blood on Ficoll-Hypaque gradient followed by separation of macrophages from lymphocytes by glass adherence. Function was assessed by ability to

phagocytose sheep erythrocytes, Latex, and *Staph. albus* by visual assessment, and uptake and cytotoxicity of <sup>51</sup>Cr labelled sheep erythrocytes.

Macrophages from patients with quiescent chronic liver disease showed significantly poorer phagocytic ability than did those in control subjects, but function was not impaired in cirrhosis with evidence of inflammatory activity (either hepatic or extra hepatic). It is suggested that peripheral macrophage function in patients with chronic liver disease is depressed, but these macrophages remain capable of responding to external stimuli.

#### Clq binding activity and complement (Clq, C3) catabolism in primary biliary cirrhosis and chronic active liver disease

H. C. THOMAS, B. J. POTTER, E. ELIAS, D. DE VILLIERS, AND S. SHERLOCK (*Department of Medicine, Royal Free Hospital, Hampstead, London*) Sera from patients with chronic active hepatitis (CALD) and primary biliary cirrhosis (PBC) were examined for immune complexes by the Clq binding assay. C3 and Clq catabolism were studied using purified trace labelled proteins.

Increased Clq binding was detected in all patient groups (control group (mean  $\pm$  SEM)  $12.9 \pm 0.6$ ; PBC  $28.6 \pm 4.1$ ; CALD (HBs +ve)  $34.4 \pm 5.1$ ; CALD (HBs -ve)  $35.1 \pm 3.3$ ). In sucrose gradient studies the Clq binding material was found in 7-10S and >20S fractions.

In PBC the fractional catabolic rate (FCR) of C3 has been shown to be increased<sup>1</sup> and in this study the FCR of Clq is also significantly raised (range 3.4 to 6.2% of plasma pool/h; normal range 1.9 to 2.9%/h). In HBs +ve CALD the FCR of C3 ranged from 2.0 to 3.5%/h (normal range 1.3 to 2.4%/h) and the FCR of Clq was also significantly increased (range 3.4 to 7.5%/h). However, in HBs -ve CALD the FCR of C3 and Clq were within the normal range.

**Conclusion** Increased concentrations of Clq binding material were found in PBC and in HBs +ve and -ve CALD. This probably indicates the presence of immune complexes. The increased catabolism of C3 and Clq in PBC and HBs +ve CALD indicates activation of the classical pathway of complement. The finding of increased Clq binding with normal catabolism of Clq and C3 in HBs -ve CALD suggests failure of activation of this pathway.

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#### Levamisole in the treatment of HBs antigen positive chronic active liver disease

R. G. CHADWICK, S. JAIN, H. C. THOMAS, AND S. SHERLOCK (*Department of Medicine, Royal Free Hospital, London*) Patients with HBs +ve CALD have decreased T cell and increased null cell concentrations. *In vitro* exposure to levamisole partially corrects this defect<sup>1</sup>. In this study we have investigated the *in vivo* effect of levamisole on T cell function and liver function in seven patients with HBs +ve CALD. Each patient was subjected to serial observations at weekly intervals over six months in an on/off/on/off designed trial.

In all patients there was a significant increase in T cell concentrations during levamisole treatment. In three patients after two to six weeks of treatment there were significant increases in transaminases and in HBs antigen titres. These rises lasted for four to six weeks and returned to control values when the drug was stopped. Four weeks later, on recommencing treatment the same changes occurred. During the period of raised transaminases, T cell concentrations (measured by E rosetting) increased and, after this, anti-core titres increased.

In four patients, although T cell concentration increased, there was no change in transaminase or HBs antigen titres. These patients were anergic to a group of skin test antigens.

**Conclusion** Levamisole resulted in increased T cell concentrations in all seven patients. In three patients who responded normally to skin test antigens, this was accompanied by increased transaminases, and increased HBs antigen titres, probably representing increased lysis of infected cells. In four patients who were anergic on skin testing, there was no response. Levamisole may therefore by its immunostimulant properties accelerate lysis of infected hepatocytes.

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#### PANCREAS

#### Diagnostic value of the oral pancreatic function test (PFT)

C. J. MITCHELL, C. S. HUMPHREY, A. W.



BULLEN, AND J. KELLEHER (*Departments of Medicine and Surgery, University of Leeds, St. James's Hospital, Leeds*) An oral PFT using the synthetic peptide N-benzoyl-L-tryrosyl-P-aminobenzoic acid (Bz-Ty-PABA) can differentiate normal subjects from patients with pancreatic disease<sup>1,2</sup>. The ingested peptide is specifically hydrolysed by chymotrypsin to liberate P-aminobenzoic acid (PABA) which is absorbed, conjugated, and excreted in the urine to provide an indirect index of exocrine pancreatic function. The diagnostic value of the test will depend upon ability to distinguish pancreatitis from intestinal disease.

We have studied urinary eight hour PABA excretion in 26 subjects after an oral dose of 2g Bz-Ty-PABA. In eight control subjects, mean PABA excretion was  $74.2 \pm 10.25$  (SD)% of ingested dose—similar to previous reports. In 10 patients with pancreatic disease (eight chronic pancreatitis, two acute relapsing pancreatitis), excretion was lower than controls at  $44.8 \pm 10.2\%$  ( $P = < 0.001$ ) with no overlap between the two groups. However, in eight patients with gastrointestinal disease (six extensive small bowel disease, two post-gastrectomy), all with normal Lundh tests and six with steatorrhoea, urinary PABA excretion was also impaired (mean  $42 \pm 25\%$ ) with only three values within the control range. The Lundh test correlated with PABA excretion in controls and pancreatic disease ( $r = 0.94$ ) but not in the gastrointestinal disease group.

We conclude that the test cannot differentiate between pancreatic and gastrointestinal disease, which is often the clinical problem.

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#### The Lundh meal and ERCP in pancreatic disease

M. G. ASHTON, A. T. R. AXON, AND D. J. LINTOTT (*University Department of Medicine, The Gastroenterology Unit and the Department of Diagnostic Radiology, Leeds General Infirmary, Leeds*) Forty patients underwent both a Lundh test and endoscopic retrograde cholangiopancreatography (ERCP) for suspected or known pancreatic disease. The Lundh test

usually preceded pancreatography and the two hour mean tryptic activity (MTA) was measured<sup>1</sup>. Pancreatogram changes were assessed retrospectively by two independent observers and classified into normal, minimal change and gross change using a modification of the criteria of Kasugai *et al.*<sup>2</sup>. A third opinion was used to arbitrate in five pancreatograms in which there was disagreement.

Of the 19 patients with normal pancreatograms, all but four had a MTA greater than 11 IU (mean  $15.4 \pm 4.0$  SD). Ten patients with minimal changes of the pancreatogram had moderate but significant depression of the MTAs (mean  $9.0 \pm 2.8$  SD) ( $P < 0.01$ ), although there was some overlap into the normal range. Eleven patients with gross pancreatogram changes had gross depression of the MTAs (mean  $3.0 \pm 1.4$  SD) ( $P < 0.01$ ).

In conclusion, there is seen to be a good correlation between the Lundh test and pancreatography but both tests are required to establish minimal change pancreatitis as the exocrine function test may be equivocal in this condition.

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#### Lactoferrin radioimmunoassay: levels in pure pancreatic juice

S. S. FEDAIL, R. F. HARVEY, P. R. SALMON, AND A. E. READ (*University Department of Medicine, Bristol Royal Infirmary, Bristol*) We have developed a radioimmunoassay for lactoferrin and used it to study the levels in pure pancreatic juice obtained endoscopically. An antiserum of high affinity and specificity was obtained by immunisation of sheep with purified lactoferrin isolated from human milk. When the antiserum is incubated at a final dilution of 1 in  $2.25 \times 10^6$  with <sup>125</sup>I-lactoferrin and a double-antibody technique used to separate free from antibody-bound lactoferrin, the assay has a sensitivity of 1 ng/ml.

We have studied 16 patients with chronic pancreatitis, nine patients with carcinoma of the pancreas, and nine control subjects being investigated for suspected pancreatic disease and later found to be normal.

The median pancreatic juice lactoferrin

level in control subjects was 65 ng/ml, range 30-308 ng/ml; in patients with chronic pancreatitis 2350 ng/ml, range 870-11400 ng/ml; and in patients with pancreatic cancer 40 ng/ml, range 10-387 ng/ml. In a single patient with both cancer and pre-existing chronic pancreatitis the lactoferrin level was high—1300 ng/ml. These results suggest that the measurement of lactoferrin levels in pure pancreatic juice may be a useful diagnostic test for pancreatic diseases.

#### Paired pancreatic function studies using pure pancreatic juice and duodenal juice

M. E. DENYER, P. B. COTTON, M. KYNE, AND A. MILLER (*Gastrointestinal Unit and Courtauld Institute of Biochemistry, The Middlesex Hospital and Medical School, London*) Thirteen patients (eight controls, five pancreatitis) underwent paired studies using two methods: pure pancreatic juice (PPJ) collection after duodenoscopic duct cannulation, and duodenal juice (DJ) using a four-lumen tube with gastric and duodenal markers. After a bolus injection of GI H secretin (1 CU/kg) in seven subjects, or an infusion of secretin and pancreozymin (1 CU/kg/h) in six subjects, 10 minute collections were made for up to 50 minutes, and analysed for volume bicarbonate and amylase. Mean volume recovery in DJ studies was 69% (range 12.5-100%). Corrected mean DJ volumes exceeded PPJ volumes by a ratio of 2.3:1 (range in normal subjects 0.45-9.6:1; in pancreatitis 1.22:1). Despite mean bicarbonate concentration being 34 mmol/l higher in PPJ than DJ (range 0-100 mmol/l), the overall bicarbonate output in DJ studies was greater (mean ratio 1.5:1; range 0.26-13.5:1). This excess includes biliary bicarbonate, but also reflects incomplete PPJ collection; mean amylase concentration and output were also slightly greater in DJ. Duodenal juice is contaminated and its analysis provides a crude assessment of pancreatic function. Pure pancreatic juice studies are difficult to perform, often incomplete, and cannot yet claim a diagnostic role.

#### Pancreatic juice analysis, carcinoembryonic antigen (CEA) and endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of pancreatic disease

D. L. CARR-LOCKE (*Department of Medicine, University of Leicester*) To define the place of pancreatic juice analysis in the diagnosis and differentiation of pancreatic

disease, ERCP has been performed and pancreatic juice cytology, volume, bicarbonate, protein, and CEA and serum CEA measured in 121 patients. Of 50 patients with pancreatic disease 24 had pancreatic cancer, 17 chronic pancreatitis, and nine acute relapsing pancreatitis, while 71 without pancreatic disease included 31 with benign obstructive jaundice, 12 with malignant disease outside the pancreas and 28 without relevant concomitant disease. Pancreatic juice flow was stimulated by a bolus injection of 50 units Boots secretin and collections made over five minutes in one minute samples.

Pancreatic juice volume, maximum and mean bicarbonate concentrations, and bicarbonate output were all significantly lower in pancreatic cancer and chronic pancreatitis, whereas pancreatic juice protein concentrations did not differ significantly between groups. Raised serum CEA correlated with the presence of obstructive jaundice rather than pancreatic disease but pancreatic juice CEA was found to be less than 110  $\mu\text{g/l}$  in all patients with a normal pancreas. Cytology gave less than 50% correct diagnoses of pancreatic cancer, whereas ERCP produced an overall accuracy of 95%.

Of the diagnostic criteria formulated, a maximum pancreatic juice bicarbonate of less than 32 mmol/l indicated pancreatic disease but a mean juice bicarbonate greater than 90 mmol/l and a five minute volume greater than 10 ml made pancreatic disease unlikely. ERCP and juice analysis together have allowed correct diagnosis in all but one patient in this study.

#### Effect of cimetidine on biliary and pancreatic function in man

D. P. MAUDGAL, D. LAWRENCE, R. BIRD, P. SANDERSON, AND T. C. NORTHFIELD (Norman Tanner Gastroenterology Unit, St. James' Hospital and Department of Medicine, St. George's Hospital Medical School, London) Intravenous metiamide reduced trypsin output in response to intravenous cholecystokinin infusion in man<sup>1</sup>. We have studied the effect of oral cimetidine therapy on jejunal tryptic activity and bile acid concentration, and on gallbladder emptying, in response to a standard Lundh meal. We have also checked whether cimetidine, by blocking gastric acid secretion, causes increased bacterial deconjugation of bile acids. Eight patients with peptic ulcer were studied before and during cimetidine treatment.

Although there was a significant rise in fourth hour breath <sup>14</sup>C<sub>2</sub> after oral <sup>14</sup>C-glycocholate, only one patient had a value above the normal range during cimetidine therapy. Thin layer chromatography for deconjugated bile acids in postprandial jejunal contents was negative in all patients. All other measurements remained within the normal range in all individuals during the study.

We conclude that oral cimetidine treatment increases bacterial deconjugation of bile acids in the small intestine, but this effect is too small to be clinically important; and that it has no significant effect on pancreatic or gallbladder function in response to food.

#### Reference

- <sup>1</sup>Thjodleifsson, B., and Wormsley, K. G. (1975). Effect of metiamide on the response to secretin and cholecystokinin in man. *Gut*, 16, 33-35.

#### *Mycoplasma pneumoniae*—an aetiological factor in acute pancreatitis?

R. FREEMAN AND M. J. MCMAHON (Public Health Laboratory, Chapel Allerton Hospital, Leeds and University Department of Surgery, The General Infirmary, Leeds) Twenty-seven cases of acute pancreatitis presenting to a surgical service were studied for serological evidence of infection with common viruses and related agents. Serum specimens were obtained on presentation and during early convalescence and tested against complement fixing antigens prepared from influenza viruses A and B, mumps virus, adenovirus, *Chlamydia psittaci*, *Coxiella burnetii*, and *Mycoplasma pneumoniae*. In addition, antibody to mumps virus was assayed by haemagglutination-inhibition, and neutralising antibodies to coxsackie viruses types B1 to B6 were measured.

Thirty-three per cent of the patients had a significant and reproducible rise in antibody to *Mycoplasma pneumoniae* over the course of their illness. No evidence of infection with any of the other agents tested was found with the exception of two patients in whom there was a rise in antibody to coxsackie virus.

A high incidence of serological evidence of infections with *Mycoplasma pneumoniae* has been previously reported in acute pancreatitis<sup>1</sup>, although it was felt possible that the antibody was autoimmune in origin. Preliminary biochemical and epidemiological studies in the Leeds area, though not conclusive, suggest the possibility that acute pancreatitis and infec-

tion with *Mycoplasma pneumoniae* may be causally related.

#### Reference

- <sup>1</sup>Leinikki, P., Pantzar, P., and Tykka, H. (1973). Antibody response in patients with acute pancreatitis to *Mycoplasma pneumoniae*. *Scandinavian Journal of Gastroenterology*, 8, 631-635.

#### Rise of secretin after oral feeding

G. R. GREENBERG, W. HÄCKI, W. DOMSCHKE, S. DOMSCHKE, P. MITZNEGG, L. DEMLING, AND S. R. BLOOM (Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, and Medizinische Klinik mit Poliklinik, Erlangen, West Germany) Secretin, the first hormone described, has been said not to have a physiological role in man. However, clarification of its importance has been hampered by the failure to demonstrate a rise after food. We therefore investigated first whether any detectable release of secretin occurs with endogenous acid stimulation, by assessing secretin levels after pentagastrin (6  $\mu\text{g/kg/h}$ ) without gastric aspiration. Secretin levels were also measured after a standard breakfast (CHO 66 g, fat 22 g, protein 18 g) and after 250 ml of an oral lemon drink (pH 2.7).

After pentagastrin ( $n = 6$ ) secretin levels increased from basal values of  $2.2 \pm 0.63$  (mean  $\pm$  SEM) pmol/l to a peak of  $7.0 \pm 1.81$  ( $P < 0.005$ ). No change occurred after control experiments with pentagastrin and gastric aspiration or with 0.9% saline.

After ingestion of the breakfast ( $n = 9$ ) a peak increase to  $5.1 \pm 0.67$  pmol/l from basal levels of  $2.5 \pm 0.34$  occurred at 45 minutes ( $P < 0.005$ ). By contrast, after drinking lemonade a more substantial mean incremental rise of 10.8 pmol/l ( $P < 0.005$ ) at four minutes was observed.

These data demonstrate that endogenous acid production releases secretin. The rise of secretin seen after food or lemonade was proportional to the duodenal acid load and adequate to stimulate pancreatic bicarbonate output<sup>1</sup>. Thus, secretin is indeed a hormone with a physiological role in man.

#### Reference

- <sup>1</sup>Häcki, W. H., Bloom, S. R., Mitznegg, P., Domschke, W., Domschke, S., Belohlavek, D., Demling, L., and Wunsch, E. (1977). Plasma secretin and pancreatic bicarbonate response to exogenous secretin in man. *Gut*, 18, 191-195.

### Half-life, clearance, and endogenous secretion rates of cholecystokinin-pancreozymin in man

R. F. HARVEY, JANE, M. OLIVER, A. E. READ, A. EDERLE, I. VANTINI, L. A. SCURO, J. F. GROARKE, AND O. FITZGERALD (*Department of Medicine and Gastroenterology Unit, Frenchay Hospital, Bristol; Department of Medicine, Bristol Royal Infirmary; III Clinica Medica Generale dell'Università di Padova, Verona; and Department of Medicine and Therapeutics, University College, Dublin*) Serum cholecystokinin-pancreozymin (CCK) levels were measured by radioimmunoassay in 10 normal subjects after a mixed meal and after infusion of cholecystokinin at two different rates. The mean serum increment during infusion of exogenous hormone was linearly related to the dose infused. After stopping the infusion, serum CCK levels fell rapidly with a half-life of 2.46 minutes and a calculated clearance rate of 9.13 ml/kg-min. For the first 30 minutes after the meal, serum levels were similar to those produced by infusion of exogenous porcine CCK at 2 Ivy dog units per kg-h, falling gradually thereafter.

Rapid injection of porcine CCK into normal subjects and patients with pancreatic diseases showed that the half-life of CCK in the circulation of such patients is not significantly different from normal.

**Conclusions** (1) Cholecystokinin-pancreozymin is cleared very rapidly from the circulation in man; (2) the raised serum CCK levels in patients with pancreatic disease are not due to decreased clearance of the hormone; (3) a 'physiological' infusion rate for CCK is approximately 2 Ivy dog units/kg-h.

### Hormonal content of commercial preparations of cholecystokinin-pancreozymin

JANE M. OLIVER AND R. F. HARVEY (*Department of Medicine, Bristol Royal Infirmary and Frenchay Hospital, Bristol*) There are two widely available commercial preparations of cholecystokinin-pancreozymin (CCK), one produced by the Boots Company Ltd., Nottingham (Boots Pancreozymin) and one by the GIH Research Laboratory, Karolinska Institute, Stockholm (GIH cholecystokinin). Although each ampoule of GIH cholecystokinin nominally contains 75 Ivy dog units of CCK and each ampoule of Boots Pancreozymin about 100 Crick Harper Raper units (theoretically equivalent to 25 Ivy dog units), we observed in clinical use that

the Boots preparation appeared to be the more potent. We have therefore studied the hormone content of these two CCK preparations in more detail.

Bioassay, using isolated strips of rabbit gall-bladder, showed Boots Pancreozymin to be approximately eight times more potent than expected.

Radioimmunoassay revealed an even larger difference between the immunoreactive content of these two hormone preparations—Boots Pancreozymin being approximately 18 times more immunoreactive than GIH CCK.

Because of these unexpectedly large discrepancies, samples of Boots Pancreozymin (batch nos. 6295, 6139, and 5833) and GIH CCK (nos. 273121, 27582, and 27633) were chromatographed on columns of sephadex G50 (Pharmacia) and the hormone content of each eluted fraction measured by radioimmunoassay.

The patterns of eluted CCK-like immunoreactivity were quite different with the two preparations. The Karolinska Institute preparations consisted mainly of peptides eluting in the positions corresponding to CCK-33 and CCK-39. In contrast, the Boots preparations were made up of fractions which eluted immediately before and after the salt peak.

**Conclusions** (1) One nominal Crick Harper Raper unit of Boots Pancreozymin is biologically approximately twice as potent as one nominal Ivy dog unit of Karolinska Institute Cholecystokinin; (2) the biological activity of Boots Pancreozymin is due largely to its content of small molecular forms of the hormone; (3) Boots Pancreozymin also contains immunoreactive forms of CCK-PZ which lack biological activity.

### PP in the assessment of pancreatic exocrine function

T. E. ADRIAN, H. S. BESTERMAN, C. N. MALLINSON, AND S. R. BLOOM (*Royal Postgraduate Medical School, Hammer-smith Hospital, and Greenwich District Hospital, London*) The cells producing pancreatic polypeptide (PP), the newest circulating hormone, are confined in man almost entirely to the pancreas. Its measurement in plasma by radioimmunoassay is straightforward and demonstrates a rapid and very substantial rise after a meal. As PP release appears to be controlled by exactly the same mechanisms that control pancreatic enzymes<sup>1</sup>, we have investigated its release in patients with two causes of steatorrhoea, chronic pan-

creatitis and coeliac disease.

A standard test breakfast was ingested by 16 healthy controls and 21 patients with chronic pancreatitis, nine having severe chronic steatorrhoea and 12 having x-ray calcification or ERCP abnormalities but no overt exocrine deficiency. Plasma PP in controls rose from  $28 \pm 7$  pmol/l to a 30 minute peak of  $166 \pm 25$  and in the patients with pancreatic disease without steatorrhoea from  $38 \pm 10$  pmol/l to  $156 \pm 32$ . In the nine subjects with exocrine deficiency PP release was grossly impaired ( $18 \pm 5$  pmol/l rising to  $44 \pm 12$  at 30 min,  $P < 0.001$ ). Injection of Boots Secretin, a previously described intravenous stimulus to PP release<sup>1</sup>, gave an exactly parallel reduction in response in the pancreatic exocrine deficiency patients.

In contrast, in 10 untreated coeliac patients with severe steatorrhoea PP release was quite normal.

Thus, measurement of PP after a test meal or intravenous Boots Secretin may form a new and convenient test in the initial assessment of steatorrhoea.

### Reference

<sup>1</sup>Adrian, T. E., Bloom, S. R., Besterman, H. S., Barnes, A. J., Cooke, T. J. C., Russell, R. C. G., and Faber, R. G. (1977). Mechanism of pancreatic polypeptide release in man. *Lancet*, 1, 161-163.

### Characterisation of secretin-like peptides from tissue and plasma extracts using immunoaffinity chromatography

J. C. MASON, R. F. MURPHY, AND K. D. BUCHANAN (*Departments of Biochemistry and Medicine, Queen's University, Belfast*) Antibodies to secretin raised in sheep and specific for a region of the hormone containing residues 14 to 27 were immobilised on CNBr-activated Sepharose 4B. Human plasma and preparations obtained by extracting porcine duodenum and jejunum with acidified ethanol were applied to the immunoaffinity columns. Non-biospecifically bound materials were eluted<sup>1</sup> with 0.15M Na Cl adjusted to pH 11. Materials which bind antibodies to secretin in radioimmunoassay were retained on the columns and were subsequently eluted with 4M guanidinium chloride. The secretin-like fractions were further characterised by gel-filtration on Sephadex G50. At least four molecular species of secretin-like peptides were detected in the intestinal preparations.

Polypeptide material with molecular weight 6000 was the predominant form



and was accompanied by peptides with molecular weight about 11 000, 3500, and <2000. Most of the secretin-like immunoreactivity from plasma, however, was detected in fractions with molecular weight <3000 though a significant proportion (10 to 20%) of the immunoreactivity had an apparent molecular weight about 12 000. The multiplicity of secretin-like peptides in the intestine and plasma is analogous to that observed for glucagon-like immunoreactivity<sup>2</sup> and may be due to the presence of precursors and degradative products of secretin.

#### References

<sup>1</sup>Murphy, R. F., Conlon, J. M., Imam, A., and Kelly, G. C. (1977). *Journal of Chromatography*, **135**, 427.

<sup>2</sup>Conlon, J. M., Flanagan, R. W. J., Buchanan, K. D., and Murphy, R. F. (1976). *Excerpta Medica*, **400**, 50.

#### GIP cells in chronic pancreatitis

A. M. J. BUCHAN, J. M. POLAK, S. R. BLOOM, H. BESTERMAN, M. SOUTH, R. MCCLOY, J. H. BARON, AND A. G. E. PEARSE (*Departments of Histochemistry, Medicine and Surgery, Royal Postgraduate Medical School, London*) Gastrin inhibitory polypeptide (GIP) is a 43 aminoacid polypeptide originally extracted from the small intestine. Although first described by its effect on gastric acid secretion, the main action of GIP appears to be in the stimulation of insulin release. The hormone has therefore been renamed Glucose dependent Insulin releasing Peptide.

Combined immunocytochemical and radioimmunoassay studies have shown that GIP is predominantly localised in the small intestine ( $71 \pm 8$  pmol/g— $12.5$  cells/mm<sup>2</sup>). Electron-immunocytochemical studies have now shown that the GIP cells correspond to the previously described K cell of the electronmicroscopic classification. Knowledge of the cell of origin of GIP and the appearance of its secretory granules could be important in GIP pathology. There is an abnormally high GIP response to an oral glucose load in patients with chronic pancreatitis<sup>1</sup>. We therefore carried out quantitative immunocytochemical and ultrastructural studies of duodenal GIP cells in biopsies from fasting patients with the disease, in order to ascertain if the high circulating GIP levels were due to a hyperplasia of normally secreting GIP cells or hypersecretion by a normal or decreased number of GIP cells. Results showed a non-significant (11.52%) decrease in the number of detectable GIP cells.

Ultrastructural studies showed smaller and more numerous secretory granules in these patients, suggesting rapid synthesis and release.

The present results indicate that GIP cells in chronic pancreatitis are not hyperplastic but may be hypersecretory and thus empty of hormone.

#### Reference

<sup>1</sup>Creutzfeldt, W., Ebert, R., Arnold, R., Frerichs, H., and Brown, J. C. (1976). Gastric inhibitory polypeptide (GIP), gastrin and insulin. Response to test meal in coeliac disease and after duodenopancreatectomy. *Diabetologia*, **12**, 279-286.

#### New view of pancreatic endocrine tumours

S. R. BLOOM, A. M. WEST, J. M. POLAK, AND T. E. ADRIAN (*Royal Postgraduate Medical School, Hammersmith Hospital, London*) Four clinically important types of pancreatic endocrine tumour have been described—secreting glucagon, insulin, gastrin, and VIP. The concept of pancreatic apudomas secreting more than one type of peptide hormone has been raised, however, and we have investigated this by radioimmunoassay and immunocytochemistry of two near pancreatic hormones, somatostatin and PP.

Significant quantities of somatostatin were found in 19 pancreatic tumours available for investigation. The highest concentration was present in the gastrinomas ( $2.2 \pm 0.7$  nmol/g,  $n = 5$ ), less in two glucagonomas (mean  $0.2$  nmol/g) and two insulinomas (mean  $0.1$  nmol/g) and only small amounts in VIPomas ( $0.004 \pm 0.002$  nmol/g,  $n = 10$ ). In many of these tumours immunofluorescent D cells were seen.

In 27 out of 69 pancreatic tumours, extracts showed a very high concentration of PP. On immunocytochemistry numerous PP cells were found in these tumours. In 60 patients fasting plasma PP concentrations were measured and were grossly raised in 26.

Thus, in a pancreatic tumour thought to be producing one type of hormone, it is common to find considerable quantities of other pancreatic hormones present. The concept of endocrine tumours being composed of a single cell type appears no longer valid. The chance predomination of one cell type is responsible for the clinical syndrome but all pancreatic endocrine tumours should now perhaps be classified under the more general heading of 'islet cell tumours'.

#### CLINICAL DIAGNOSTIC

#### Assessment of nutrition in surgical patients—a comparison of simple anthropometry with measurement of total body nitrogen from neutron activation analysis

J. P. COLLINS, G. L. HILL, J. A. BRADLEY, I. MCCARTHY, C. B. OXBY, AND L. BURKINSHAW (*University Departments of Surgery and Medical Physics, The General Infirmary, Leeds*) There is increasing interest in the use of arm circumference, triceps skinfold, and derivatives of these for nutritional assessment of muscle and fat reserves in surgical patients. In order to study the relationships of these measurements to body cell mass we measured body weight, skinfold thickness (mid-biceps, mid-triceps, subscapular, suprailliac) arm circumference and total body nitrogen (TBN) by *in vivo* neutron activation analysis on nine controls, 12 surgical patients with minimal weight loss (3-4%) and 12 patients with major weight loss (17-31%). Values for fat free mass, arm muscle circumference, and arm muscle area were calculated from these values and compared with those of TBN.

TBN correlated well with all the anthropometric values except triceps skinfold. The correlation coefficients were for fat free mass ( $r = 0.90$ ), for body weight ( $r = 0.83$ ), for arm muscle circumference ( $r = 0.78$ ), for arm muscle area ( $r = 0.77$ ), and for arm circumference ( $r = 0.71$ ).

It is concluded that fat free mass, body weight, arm muscle circumference, and arm circumference are reasonable indicators of body cell mass. Although anthropometry lacks the precision to be clinically useful for individual patients, these measurements are of value when groups of patients are being compared.

#### Use of the creatinine-height index in underweight patients

A. J. RICH, D. TREGONING, T. HAWKINS, AND P. D. WRIGHT (PROFESSOR I. D. A. JOHNSTON) (*Departments of Surgery and Medical Physics, University of Newcastle upon Tyne*) The creatinine-height index (CHI) has been proposed by several authors<sup>1,2</sup> as an indicator of changes in lean body mass in normal individuals and during nutritional support. However, creatinine metabolism in illness is not fully understood and even in normal individuals Greenblatt *et al.*<sup>3</sup> recorded considerable individual daily variation in urinary creatinine excretion.

Two groups of patients were studied. Group I were 15% or more below their ideal weight. Group II were patients with colorectal cancer and were within 15% of their ideal weight. Anthropometric measurements were used to calculate the arm muscle circumference for each patient. Total body potassium was measured using a whole body counter and urinary creatinine used to calculate the CHI. The results were compared with values for normal individuals described elsewhere<sup>1</sup>.

Analysis of the results showed that a better estimate of lean body mass as measured by total body potassium was obtained using arm muscle circumference than by the CHI. Urinary creatinine excretion showed marked variation on a day-to-day basis and more consistently underestimated lean body mass in group I than in group II.

It is suggested that the CHI as calculated from a single 24-hour urinary collection is unlikely to reflect accurately the lean body mass in an underweight patient. As a single, simple measurement the arm muscle circumference is more likely to be accurate, provided clinical oedema is absent.

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#### Biopsy evidence of hyperplasia of Brunner's glands

Z. MAŘATKA, J. KOČIÁNOVÁ, P. JIRKO, AND J. KUDRMANN (*Hospital Bulovka, Prague, Czechoslovakia*) Hyperplasia of Brunner's glands (HBg—diffuse or nodular) means increased thickness of their layer in duodenal submucosa. A reliable diagnosis can be made only by measuring in postmortem or surgical specimens of the entire wall. In a postmortem study of 100 unselected specimens the average thickness in descending duodenum was 0.42 mm; thickness over 0.6 HBg was found in 16%. Simultaneously other changes were noted: marked lobularity and septalisation, penetrating into the mucosa, fenestration and fragmentation of muscularis mucosae, displacement of Lieberkühn's glands. This

syndrome of histological changes was then identified in aspiration biopsy specimens and termed 'biopsy evidence of hyperplasia of Brunner's glands' HBg. Among 260 unselected gastrointestinal patients HBg was established in 10. Statistically significant correlation was found between HBg and polypoid x-ray pattern as well as nodular appearance upon duodenoscopy. However, these appearances were absent in hypotonic duodenography and surgical exploration in most cases. It is concluded that polypoid x-ray and endoscopic pattern is rarely caused by hyperplastic glands themselves; more often it is caused by mucosal folds caused by irregular contraction of the muscularis mucosae disrupted by protruding glands. Most patients with HBg and polypoid pattern had mild histological duodenitis and some sort of epigastric distress.

#### Plasma binding, renal and biliary excretion of two intravenous cholangiographic agents in normal and jaundiced subjects

J. DORAN, W. VENNART, AND G. D. BELL (*University Department of Therapeutics and Department of Medical Physics, City Hospital, Nottingham*) A new intravenous cholangiographic agent, iotroxamide (I<sub>T</sub>)\* has recently been produced. It is claimed that I<sub>T</sub> gives better opacification of the bile duct, is less protein bound, and produces less side-effects than either ioglycamide (I<sub>G</sub>) or iodipamide.

Biliary iodine concentration achieved during T-tube drainage after cholecystectomy was compared in eight patients (mean bilirubin 54.3 μmol/l, range 7-142). Each patient received both agents, the infusions being given on the ninth and 11th post-operative days and the order of infusion being randomly allocated. In all the patients studied the maximum biliary iodine concentration was greater using iotroxamide than with ioglycamide, the average difference being 28% (paired Student's *t* test, *P* < 0.01).

We have also studied the plasma binding and renal excretion of radio-labelled I<sub>T</sub> in six normal and six jaundiced subjects and compared the results with those obtained in a similar number of patients given I<sub>G</sub>. No significant difference was observed between I<sub>T</sub> and I<sub>G</sub>. However, with both compounds the plasma binding was reduced (*P* < 0.05) and the renal excretion increased (*P* < 0.01) in the presence of jaundice.

**Conclusion** (1) Bilirubin displaces I<sub>T</sub> and

I<sub>G</sub> molecules from their binding sites on albumin and, as a result, their renal excretion is increased in the presence of jaundice; (2) I<sub>T</sub> should prove superior to I<sub>G</sub> as a cholangiographic agent.

\*Schering Chemicals, Ltd. SH H 273 AB

#### Urinary urobilinogen—should we be measuring it?

I. T. GILMORE, A. C. PEATFIELD, AND R. P. H. THOMPSON (*G.I. Laboratory, Rayne Institute, St. Thomas' Hospital, London*) The semiquantitative measurement of the concentration of urobilinogen in urine with dipsticks is said to be a sensitive test of liver function and is probably the most widely used. We are reassessing its practical value, and have compared Ehrlich's aldehyde reagent (EAR) with a new, more specific chromogen, *p*-methoxybenzenediazonium-fluoborate<sup>1</sup> (p-MDFB), available also in dipstick form as 'B.M. test urobilinogen'.

Nine patients with active chronic hepatitis (ACH) in and out of control were studied fortnightly for one year with urinary urobilinogens and conventional liver function tests (LFT). There was a poor correlation between biochemical relapses and urobilinogen, but the latter was sometimes raised when LFT were normal. Urobilinogen was also variable in patients with viral hepatitis, but tended to be increased early and late in the illness. Results with EAR and p-MDFB methods were similar, but B.M. test urobilinogen sticks and Urobilistix correlated poorly with either.

We conclude that (1) testing with dipsticks should be abandoned; (2) urinary urobilinogen levels may be raised in ACH when other liver function tests are normal but is probably not a useful routine test; (3) p-MDFB test for urobilinogen compares favourably with Ehrlich's reagent.

#### Reference

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#### Grey scale ultrasonography in diagnosing gall stones

A. J. MCKAY, J. G. DUNCAN, S. N. JOFFE, C. W. IMRIE, AND L. H. BLUMGART (*University Department of Surgery and Department of Radiology, Royal Infirmary, Glasgow*) Grey scale ultrasonography (GSU) has been assessed prospectively in

100 patients in three clinical situations where diagnosis by conventional contrast radiology often fails<sup>1</sup>. The diagnosis of gall stones in each patient was subsequently confirmed by cholangiography and/or surgery. GSU was performed within 48 hours of admission in 30 patients with suspected acute cholecystitis. The gall bladder was outlined in 87% and stones shown in 18 patients. In 30 outpatients investigated for recurrent biliary colic, the gall bladder was demonstrated in 83%, and gall stones reported in 15, with only one false positive.

In 40 patients with acute pancreatitis, GSU was carried out within one week of admission and outlined the gall bladder in 72.5%. In 13 patients gall stones were accurately diagnosed with two false positive results. Patients required no preparation for the investigation and the presence of gas obscuring the ultrasound image was the main cause of technical failure.

The early and accurate diagnosis of gall stones in acute cholecystitis, biliary colic and acute pancreatitis will lead to an improved selection of patients for definitive surgery.

#### Reference

- <sup>1</sup>Raine, P. A. M., and Gunn, A. A. (1975). Acute cholecystitis. *British Journal of Surgery*, 62, 697-700.

#### Ultrasound and cholecystography in the diagnosis of acute cholecystitis

J. G. MOSLEY, C. METROVELI, AND A. GREGORY (introduced by J. SPENCER) (*Departments of Surgery and Radiology, Royal Postgraduate Medical School, London*) Acute cholecystitis is one of the major causes of emergency surgical admission, and there is evidence that cholecystectomy within three or four days of admission reduces the duration of stay in hospital without increasing morbidity<sup>1</sup>. Unfortunately, accurate diagnosis in the acute situation is often difficult.

We report a consecutive series of 34 emergency admission with a clinical diagnosis of acute cholecystitis. They were investigated within 48 hours of admission by oral cholecystography, B mode scanning equipped with grey scaling and more recently also cholecystography using intravenous <sup>99m</sup>Tc pyridoxylidene glutamate<sup>2</sup>. The findings were subsequently verified by further radiography or laparotomy.

Oral cholecystography gave the correct diagnosis in 79% of cases and was

unsatisfactory in 21%. B scanning was correct in 82%, incorrect in 9%, and unsatisfactory in 9%. Cholecystography gave the correct diagnosis in eight patients investigated.

The results indicate that scanning (which is considerably more comfortable for the patient), is comparable with oral cholecystography in the diagnosis of acute cholecystitis. Our preliminary findings also indicate that cholecystography is a rapid procedure acceptable to patients which may be very useful in diagnosis.

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#### Vitamin B<sub>12</sub> binding protein in hepatocellular carcinoma: value in monitoring therapy

S. P. KANE, J. KOHN, P. JOHNSON, R. WILLIAMS, AND I. M. MURRAY-LYON (*Department of Gastroenterology, Charing Cross Hospital; Department of Chemical Pathology, Queen Mary's Hospital; Liver Unit, King's College Hospital*) Previous workers<sup>1</sup> have demonstrated high serum and tumour levels of an abnormal vitamin B<sub>12</sub> binding glycoprotein in three adolescents with malignant hepatoma.

We have used the serum unsaturated vitamin B<sub>12</sub> binding capacity (UB<sub>12</sub>BC) measured by radio-assay<sup>2</sup> as an index of circulating vitamin B<sub>12</sub> binding protein levels. This assay was employed to monitor the progress of two juveniles with high plasma levels during intermittent chemotherapy with adriamycin. Both patients had a biopsy-proven hepatocellular carcinoma and sera were negative for HBsAg and alpha fetoprotein. The 15 year old girl's UB<sub>12</sub>BC at the onset of treatment was 414 µg/l (normal range—0.83-1.7 µg/l) and it rose during three months to 828 µg/ml in parallel with a deterioration in her clinical state and biochemical indices. The 16 year old boy's initial UB<sub>12</sub>BC was 132 µg/l, falling to 79 µg/l after three courses of chemotherapy which resulted in some decrease in hepatomegaly. UB<sub>12</sub>BC levels rose again to 138 µg/l as his disease progressed.

We have screened the sera of 39 adult patients aged 19-71 years with hepatocellular carcinoma for evidence of a gross

rise in UB<sub>12</sub>BC. The range found was 0.09 to 6.1 µg/l, and only four values were above the normal range.

Assay of UB<sub>12</sub>BC thus provides a simple method of monitoring treatment in patients with hepatocellular carcinoma in whom alpha fetoprotein levels are normal. It is unlikely to prove useful in adult patients as plasma levels are not significantly raised.

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#### Breath hydrogen after lactulose as a diagnostic test for bacterial overgrowth

J. M. RHODES, D. P. JEWELL, AND P. MIDDLETON (*Department of Medicine, Royal Free Hospital, London*) The lactulose breath test<sup>1</sup> has been compared with the C<sub>14</sub> glycocholate breath test<sup>2</sup> in the assessment of suspected bacterial overgrowth of the small intestine. Seventeen patients have been studied: nine with small bowel diverticula or fistulae, five with Crohn's disease of the small bowel, one with small bowel lymphoma, and one with partial ileal resection.

Twenty millilitres of lactulose syrup were given to fasting patients. End-expiratory breath samples were analysed for hydrogen using gas chromatography. The C<sub>14</sub> glycocholate breath test was that reviewed by James *et al.*<sup>2</sup>. Samples for bacteriology were obtained by using sterile anaerobic techniques and cultured for aerobes and anaerobes.

Ten patients were normal on both tests. After lactulose four patients showed early hydrogen excretion appearing before the main peak corresponding to the passage of lactulose into the colon. All four had abnormal C<sub>14</sub> glycocholate tests. Three patients with abnormal C<sub>14</sub> glycocholate tests had no early hydrogen excretion and were all known to have ileal disease likely to cause bile-salt malabsorption. The absence of overgrowth was confirmed bacteriologically in these cases.

The lactulose breath test, therefore, is successful in diagnosing small bowel overgrowth and in distinguishing this from



ileal disease; this gives it a useful advantage over the C<sub>14</sub> glycocholate breath test.

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#### Fluorescent antibody studies in giardiasis

S. G. WRIGHT, A. H. MOODY, A. M. TOMKINS, D. S. RIDLEY (*Hospital for Tropical Diseases, London, Department of Human Nutrition, London School of Hygiene and Tropical Medicine, London*) Giardiasis is a protozoan infection of the gastrointestinal tract that usually produces no symptoms but in a proportion of patients is associated with malabsorption that resolves after appropriate treatment<sup>1</sup>. Parasitological diagnosis is usually straightforward but in some patients with marked symptoms and considerably disordered absorption the parasite can be elusive. The fluorescent antibody test for giardiasis<sup>2</sup> using *Giardia lamblia* cysts as antigen was evaluated in sera from patients with a variety of intestinal disorders.

The test was positive in 18 out of 19 cases of giardiasis with malabsorption in reciprocal titres ranging from 20 to 320. Negative results were obtained in control subjects (20), gluten enteropathy (eight cases), inflammatory bowel diseases (12 cases), and in 10 of 11 eleven patients with acute tropical sprue. This test appears useful in the investigation of patients with malabsorption.

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#### Rectal IgE cells in inflammatory bowel disease

D. P. O'DONOGHUE AND PARVEEN J. KUMAR (*Department of Gastroenterology, St. Bartholomew's Hospital, London*) The differentiation between Crohn's colitis and ulcerative colitis (UC) is often difficult and immunological studies have to date been unhelpful in separating the two conditions. Recently Heatley and colleagues<sup>1</sup> have shown an increase in IgE-containing cells

in the rectal mucosa of patients with 'proctitis' suggesting that a local allergic response may be important in the pathogenesis of this disorder. In order to investigate if a similar mechanism might be involved in Crohn's disease (CD) and ulcerative colitis and to see if the presence of rectal IgE-cells would help differentiate these two conditions, we have studied the immunoglobulin-containing cells in rectal mucosa in patients with non-specific inflammatory bowel disease. Immunofluorescent techniques were employed.

Rectal biopsies were obtained from 15 patients with Crohn's disease who had rectal involvement, 12 with UC and these were compared with 15 control subjects. No difference was found for IgA, IgM, or IgG cells in either disease group as compared with controls. The few patients who had reduced IgA or IgM cell counts had greatly increased extracellular staining implying secretion of immunoglobulin rather than a true deficiency. IgE cells were rarely seen in control subjects but were present in large numbers in nine of 12 UC patients and seven of 15 with CD. These counts did not correlate with extent, duration, or treatment of the disease nor was there any difference within disease groups.

These findings suggest that an allergic mechanism may be important in both CD and UC.

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#### Biopsy diagnosis of infective colitis

D. W. DAY, B. K. MANDAL, AND B. C. MORSON (*St. Mark's Hospital, London, and Monsall Hospital, Manchester*) Infection by salmonella organisms of food-poisoning type not uncommonly give rise to a dysenteric type of illness, with bloody diarrhoea, tenesmus, and tenderness over the sigmoid colon<sup>1</sup>. Rectal biopsies were studied from 29 patients with salmonella colitis, seven of whom were subsequently found to have idiopathic inflammatory bowel disease. The biopsies from patients with salmonella infection alone showed changes of varying severity with mucosal oedema, polymorphs in the lamina propria, and infiltrating crypt epithelium, but, in the majority, no increase in chronic inflammatory cells and preservation of crypt architecture and mucus content. In those with the most severe

changes, crypt abscesses were seen with focal mucus depletion. These appearances are seen in other types of infective colitis including shigella dysentery, gonococcal proctitis, and amoebic colitis.

The pattern of inflammation in infective colitis is sufficiently distinctive for the histopathologist to be able to differentiate it from the appearances seen in rectal biopsies from patients with idiopathic inflammatory bowel disease. In the seven patients with coincidental salmonella infection, four have ulcerative colitis, two have Crohn's disease, and in one the diagnosis remains equivocal. In general, the histology in these cases was of the idiopathic inflammatory bowel disease.

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#### Sensitivity of gastric and colorectal cancers to cytotoxic drugs in culture

I. L. ROSENBERG, T. W. HANNAM, AND G. R. GILES (*University Department of Surgery, St. James's University Hospital, Leeds*) Cytotoxic chemotherapy for gastrointestinal cancer is usually prescribed on an empirical basis. Improved selection of drugs may follow the use of chemosensitivity tests on *in vitro* cultures of tumour cells. Twenty-five short-term monolayer cultures were successfully established from eight of 15 gastric cancers (53%) and 17 of 59 colorectal cancers (29%). Failure to culture resulted from bacterial or fibroblast overgrowth. Successful cultures were inoculated into microtitre plates and exposed to 5-fluorouracil, 1-phenylalanine mustard, methotrexate, thiotepa, cyclophosphamide, vincristine, and doxorubicin in appropriate concentrations. Defining a response as a 50% inhibition of tritiated leucine incorporation, doxorubicin appeared most active (12/25) compared with 5-FU (8/25) and vincristine (7/25), with no activity demonstrated by cyclophosphamide. Only two cultures were sensitive to four or more drugs; 12 were sensitive to one or two different drugs and six were insensitive to any.

With the exception of doxorubicin sensitivity, the degree of drug activity in culture was similar to that seen in clinical practice. Since most cultures respond to only one or two drugs, a degree of selectivity in the tests is apparent. The study suggests that a clinical application of this approach may be justifiable.

### Cell kinetic and cyclic amp studies in colorectal carcinoma—a guide to earlier diagnosis?

D. TREGONING, G. TURNER, A. J. WATSON, D. C. BRITTON, G. BONE, AND A. L. LATNER (*Departments of Surgery, Clinical Biochemistry and Clinical Pathology, University of Newcastle upon Tyne*) The Medical Research Council has indicated that colonoscopy and biological tumour markers are areas of the highest priority in the study of colorectal cancer<sup>1</sup>.

Colonoscopic mucosal biopsies were obtained from patients with adenocarcinomas of the colon, and cell kinetics and cyclic nucleotide estimations were undertaken in order to investigate the natural history of colonic cancer and thus hopefully facilitate earlier diagnosis of this common condition.

The mean mitotic index of the caecal mucosa of six normal patients was 5.9% (SD ± 0.56). This was significantly higher than that of the rest of the colon—mean 3.6% (SD ± 0.1) ( $P = 0.03$  Mann Whitney u-test).

The mean mitotic index of 19 rectal tumours was 1.1% (SD ± 0.35) and this was lower than that of normal rectal mucosa—mean 3.2% (SD ± 0.78) (Mann Whitney u-test  $P = 0.001$ ). Intrinsic mucosal differences therefore exist in different parts of the normal colon and these may be a factor in the anatomical distribution of colonic cancer.

Cyclic amp is an important determinant of cell growth and differentiation and hence may be a biological marker of colonic cancer. The mean cyclic amp concentration in 11 patients with rectal carcinoma was found to be 1.1 pmol per mg (SD ± 0.2) for the malignant tissue and 0.78 pmol per mg (SD ± 0.2) for the adjacent normal mucosa (Wilcoxon matched pairs and signed ranks test,  $P = 0.03$ ). Exploitation of these different levels of cyclic amp in normal and malignant tissue may lead to the discovery of a reliable biological marker.

#### Reference

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#### CLINICAL MEDICAL II

### Questionnaire on management of acute bleeding

G. E. THOMAS, P. B. COTTON, AND C. G. CLARK (*Gastrointestinal Unit, The*

*Middlesex Hospital, London, and Department of Surgery, University College Hospital, London*) Replies from 154 centres, representing 262 named BSG members, revealed considerable variations in opinions and practice. Only 29% of respondents controlled management of more than 80% of all bleeders admitted. Physicians constituted 96% of admitting teams; 40% of centres never used intensive therapy areas. Investigation within 24 hours was usual (severe bleeders 98%, moderate 80%, minor 47%). Endoscopy was the most accessible investigation, and was used first in 82% of centres. Double contrast bariums and urgent angiograms were rarely available. Serous complications were experienced by 14% of endoscopists. Twenty-seven per cent of respondents (34% of physicians, 8% of surgeons) did not know if a precise diagnosis helped, and 28% would withhold endoscopy for a controlled trial. Direct non-surgical treatment was rarely used (angiographic 15%, endoscopic 7%). Most respondents believed that ulcer re-bleeding was commoner in men and the elderly, and were considerably influenced towards surgery by increasing age and a previous bleed, less by ulcer size or previous dyspepsia. Questions concerning indications for surgery and its type in hypothetical patients bleeding from chronic ulcers and acute erosions revealed many major disagreements. This lack of consensus suggests a need for specific treatment trials.

### Impact of endoscopy on the outcome and management of upper gastrointestinal bleeding

G. B. LEE, P. M. SMITH, AND D. J. T. WEBSTER (*Departments of Medicine and Surgery, Llandough Hospital, Nr. Penarth, S. Glamorgan*) It is generally assumed<sup>1,2</sup> that endoscopy, by providing a quicker and more accurate diagnosis, will improve the prognosis of patients with upper gastrointestinal bleeding. We have examined this assumption by comparing patients of comparable age admitted to Llandough Hospital over two consecutive three-year periods, 1970-73, and 1973-76. An emergency endoscopy service came into being at the start of the second three-year period.

Ninety-eight patients were admitted with a diagnosis of upper gastrointestinal bleeding from 1970-73, and 151 patients from 1973-76. One hundred and eight of the latter group underwent endoscopy.

The average duration of stay in hospital fell slightly from a mean of 14.8 days to 13.0 days. Blood transfusion requirements were not significantly affected (2.5 v 2.7 units), but in 87% a bleeding site was identified, as opposed to only 55% in the earlier group. The diagnosis was also made more quickly (2.0 v 4.1 days) and surgery was performed earlier and more frequently (32% v 9%). Despite this, the overall mortality was not improved. It is concluded that endoscopy has had no effect on the prognosis of upper gastrointestinal bleeding, although the diagnostic yield is higher.

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### Early endoscopy in the prediction of further haemorrhage from peptic ulcers

D. N. FOSTER, K. J. A. MILOSZEWSKI, AND M. S. LOSOWSKY (*Department of Medicine, University of Leeds, St. James's Hospital, Leeds*) Despite the recent explosion in the use of endoscopy in upper gastrointestinal haemorrhage (UGIH) there is a dearth of documentation of the detailed findings unique to endoscopy. In most studies the lesion seen is accepted uncritically as the source of bleeding and few record the proportion of lesions bearing the stigmata of recent haemorrhage (SRH), the potential value of which in predicting the clinical course has thus been ignored.

Early endoscopy in 245 of 277 consecutive episodes of suspected UGIH managed by our unit revealed duodenal ulcers (DU) alone in 48 and gastric ulcers (GU) alone in 41, of which 27 (56%) and 33 (80%) respectively bore SRH. In the absence of SRH, only one patient with DU and none with GU had further haemorrhage (FH) or emergency surgery (ES). In contrast, where SRH were present 16 of 27 DU patients (59%) and 15 of 33 GU patients (45%) required ES.

The presence (or absence) of SRH is superior to and enhances the value of any other factor commonly used to predict the likelihood of FH from peptic ulcers and the need for ES. Early endoscopy may thus have prognostic as well as diagnostic functions in UGIH.

### Cimetidine—an advance in gastric ulcer treatment?

W. A. F. MCADAM, A. G. MORGAN, C.

PACSOO, B. E. WALKER, AND A. V. SIMMONS (*Airedale General Hospital, Steeton; Chapel Allerton Hospital, Leeds*) The use of oral cimetidine (1 g/day) has been compared with carbenoxolone (100 mg tds for one week, and then 50 mg tds) for patients under 60 years of age, and Caved-S (two tablets tds) for those over 60 years with gastric ulceration.

Initially, all patients were endoscoped, and the ulcer healing assessed either endoscopically or radiologically at monthly intervals ( $\times 3$ ). Healing was always confirmed endoscopically.

Forty-nine patients entered the study, 42 have completed, and a further three withdrawn (one cimetidine rash; two treatment failures).

**Under 60's** Five patients received cimetidine, two healed by one month, and all by two months.

Seven patients received carbenoxolone, but two were withdrawn for uncontrolled dyspepsia (at two and seven weeks), three healed by one month, four by two months and one remained unhealed at three months.

**Over 60's** Sixteen patients received cimetidine, eight healed by one month, 14 by two months and all by three months.

Fourteen patients received Caved-S, seven healed by one month, 11 by two months and all by three months.

After healing, all patients were reassessed at three monthly intervals, and to date eight have recurred.

These results suggest that, in gastric ulceration, cimetidine has equivalent healing properties to both carbenoxolone and Caved-S. A high recurrence rate in all treatment groups is noted.

#### Biliary and faecal bile acid composition in liver disease

N. KRASNER, S. T. ATHERTON, L. M. NELSON, H. FLEMING, AND R. I. RUSSELL (*Gastroenterology Unit, Royal Infirmary, Glasgow*) Disturbances of bile acid metabolism and particularly of deoxycholate metabolism have been documented in patients with alcoholic cirrhosis<sup>1,2</sup>. However, little attention has been directed to the role of alcohol in the development of bile acid abnormalities in cirrhosis of differing aetiology. Biliary and faecal bile acid composition was determined in eight patients with non-cirrhotic alcoholic liver disease (ANC), 23 with alcoholic cirrhosis (AC), seven with cirrhosis with chronic active hepatitis (CAH) and in six healthy control volunteers.

The proportion of deoxycholic acid in bile and faeces was significantly reduced in AC compared with controls ( $P < 0.01$  for bile and faeces) but there was no significant difference between AC and CAH groups. The proportion of chenodeoxycholic acid in bile and faeces was significantly greater in AC than in controls ( $P < 0.05$  in both cases) and again the AC and CAH groups were not significantly different. Values for these two bile acids in the ANC group were similar to those found in the control group but significantly different from patients with AC (deoxycholic  $P < 0.01$ ,  $P < 0.02$  chenodeoxycholic;  $P < 0.01$  for bile and faeces). The proportions of cholic acid and lithocholic acid did not differ significantly between the controls and the other groups.

We conclude that within the groups studied the presence of cirrhosis is of greater importance than the alcohol aetiology in the development of di-hydroxy bile acid disturbances.

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#### Diazepam kinetics and sedation in chronic liver disease

J. B. MCCONNELL, M. DAVIS, S. CURRY, AND ROGER WILLIAMS (*Liver Unit, King's College Hospital and Medical School, London, Department of Clinical Pharmacology, London Hospital, London*) Diazepam is the sedative of choice for endoscopy and other investigative procedures, but patients with liver disease may be unduly susceptible to its effects. In the present study we have investigated possible factors governing clinical response to an intravenous bolus dose of diazepam (0.25 mg/kg) in 12 patients with chronic liver disease and age/sex matched controls.

In patients metabolic clearance rate (MCR) for diazepam was impaired (range 0.76-4.27 l/h, controls 1.07-6.12). However, overall there was no difference from paired controls in the degree and duration of sedation, assessed by psychometric tests including Reitan trail, digit symbol substitution, card sorting, and short-term memory tests. Sedation did not correlate with diazepam MCR or serum albumin, but performance in psychometric tests,

especially the Reitan trail test, just before diazepam administration, was of value in predicting the degree of deterioration ( $r = 0.82$  for trail test). This was the case regardless of previous episodes of encephalopathy.

It is concluded that susceptibility to diazepam in chronic liver disease is increased only when cerebral function is already impaired, and the results indicate a role for increased CNS sensitivity rather than impaired drug metabolism. A Reitan trail test performed just before administration of diazepam is a useful and simple test for predicting response.

#### Social toll of Crohn's disease

B. G. GAZZARD, H. L. PRICE, AND A. M. DAWSON (*Department of Gastroenterology, St. Bartholomew's Hospital, London*) Eighty-five patients with long standing Crohn's disease were interviewed concerning their knowledge of Crohn's disease, their aspirations, and various aspects of their social life. These factors were correlated with the activity of the disease, and the psychological makeup of the patient assessed by the Eysenck personality questionnaire and the morbid anxiety index.

The men, unlike the women, were more introverted and neurotic than a control group. Twenty-eight patients with the highest score for neuroticism were being treated for depression. Neuroticism rather than activity of the disease was found to correlate with subjective feelings of illness, time off work, worries about health, and doubts about the future.

Despite periods of up to two years' sick leave, only five patients had retired through ill health and required social assistance. Of the 70 married patients 19 felt their relationship had grown closer through illness and only nine said it had become worse, despite the diminution in frequency of sexual intercourse in most couples and its cessation in 12. Extroversion rather than disease activity appeared to be the main determinant for a successful marriage.

The main conclusion was that patients adapted remarkably well to this life-long disease, despite being aware of the probability of relapse. This success was dependent on their personality rather than the extent and activity of the disease.

#### Clinical studies on abetalipoproteinaemia

P. MILLS, F. BALLANTYNE, A. FLECK, R. J.



HOLDEN, W. FOULDS, AND G. WATKINSON (*Western and Royal Infirmarys, Glasgow*) Two new cases of this rare inherited metabolic disorder are presented<sup>1</sup>. They are both female aged 36 and 46 years, demonstrating all five features of the syndrome—namely, absent low-density lipoproteins, steatorrhoea, acanthocytosis of red cells, spinocerebellar ataxia, and retinitis pigmentosa.

The basic biochemical defect of lipoprotein metabolism remains unresolved. Serum is clear, containing very low levels of cholesterol and triglyceride. At lipoprotein electrophoresis there is absence of all low-density lipoprotein including  $\beta$ , pre- $\beta$  lipoproteins, and chylomicrons. Only  $\alpha$  lipoprotein (HDL) is present in significant amounts. We have demonstrated abnormality in apolipoproteins by polyacrylamide gel electrophoresis of tetramethylurea soluble apolipoproteins<sup>2</sup>. There is markedly decreased apo-CIII<sub>1</sub> in HDL and abnormal apolipoproteins in the little remaining low-density lipoprotein.

Abnormal fat transport would be expected from these lipoprotein abnormalities. Triglyceride accumulates in intestinal mucosal cells failing to be incorporated into chylomicrons and transported into lymph vessels<sup>3</sup>. This results in malabsorption of long-chain fatty acids and fat-soluble vitamins. Both patients were deficient in Vitamins A and E and essential fatty acids.

The clinical illness may be due to malabsorption of these essential fats. We demonstrated an improvement in retinal responses within 24 hours of a Vitamin A injection, but prolonged vitamin deficiency had led to irreversible damage. We hope to prevent further deterioration by using vitamin and fatty acid supplements.

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#### Factors affecting the incidence and treatment of post-vagotomy diarrhoea

T. V. TAYLOR, M. E. LAMBERT, AND B. TORRANCE (*Manchester Royal Infirmary*) Although duodenal ulceration and gall stones are common conditions, there is no reference to the clinical results of vagotomy, pyloroplasty, and cholecystectomy performed in the same patient. From a total of 589 vagotomies performed over a

six year period, 60 patients in whom a cholecystectomy was performed were compared with two groups of 60 age- and sex-matched controls who had undergone vagotomy and pyloroplasty alone or cholecystectomy alone. Post-vagotomy diarrhoea (PVD) was present at two to three months in 48.3% after the combined operations and in 11.6% after vagotomy and pyloroplasty alone ( $p = 0.00013$ ).

The incidence in the combined group fell to 16% at two years which was comparable with the rate of resolution of PVD after vagotomy and pyloroplasty alone. Different time relations between the operations in the combined group had no significant effect on the incidence of PVD.

Cholestyramine (4g tds) was more effective in treating PVD in 16 patients after the combined operations than in 15 patients after vagotomy and pyloroplasty alone ( $p = 0.044$ ), but diarrhoea returned on withdrawal of this treatment. Cholestyramine was more effective in the treatment of PVD in these patients than aluminium hydroxide<sup>1</sup> or Lomotil. Propranolol which has been reported to inhibit the stimulatory effect of bile acid on colonic mucosa<sup>2</sup> was of no value in the treatment of PVD.

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#### Gastrointestinal (GI) hormones in non-endocrine cancers

JOY ARDILL, MAIREAD O'HARE, J. MCFARLAND, OLIVE HARVEY, J. SLOAN, P. TITTINGERTON, R. F. MURPHY, AND K. D. BUCHANAN (*Departments of Medicine, Pathology and Biochemistry, Queen's University of Belfast*) Ectopic hormone production in tumours of non-endocrine origin producing clinical syndromes is well recognised but less known is the incidence of ectopic hormone production in subclinical amounts. This is a preliminary report of a survey of unselected malignant cancers of their content of GI hormones.

Immunoreactive insulin (IRI), glucagon-like immunoreactivity (GLI), immunoreactive gastrin (IRGa), and secretin (IRS) were measured by radioimmunoassay (RIA) in aqueous extracts (IRGa) and

acid-ethanol extracts (IRI, GLI, and IRS) of the tumours. In most instances, the tumours were also prepared for specific immunoperoxidase histochemistry. Of the 35 tumours investigated 20 were lung carcinomas and 15 from various sites in the GI tract. Attempts were made to control the study, using tissue taken adjacent to the tumours and from biopsies and tissues from other operations in patients without cancer. Six of the lung tumours, a rectal carcinoma, and an oesophageal carcinoma showed significant levels of IRGa, but none of the other hormones was raised. Immunohistochemical studies confirmed the RIA data.

Therefore, IRGa production in cancers is not uncommon, although in this preliminary survey other GI hormones were not involved. In most, but possibly not in all cases, the production of IRGa is insufficient to produce clinical features but the importance of such hormone production in the aetiology, progression, and diagnostic spectrum of cancer remains to be elucidated.

#### Lethal familial protracted diarrhoea of undetermined cause: a report of 22 cases

D. C. A. CANDY, V. LARCHER, D. J. S. CAMERON, A. P. NORMAN, AND J. T. HARRIES (*The Hospital for Sick Children, Great Ormond Street, and Institute of Child Health, Guilford Street, London*) We present 22 cases (10 girls; 12 boys) of severe protracted diarrhoea in whom, despite intensive investigation, a definitive diagnosis could not be established. Eighteen patients (82%), including all four children of a consanguineous marriage, died. No such series has been previously reported.

The patients had a number of features in common: (1) Familial pattern: there was a high familial incidence of affected cases; there were normal siblings in three families, and normal offspring from three parents' previous marriages; there were two sibships from first cousin marriages. Associated extraintestinal congenital malformations were not uncommon. (2) Course of illness: onset within first few weeks of life with relentless deterioration and death after several months. (3) Stool volume: 'cholera-like' (up to 2 litres per 24 hours). (4) Pathology: small intestinal biopsy showed partial or subtotal villous atrophy; rectal biopsy showed non-specific inflammatory changes. (5) Response to dietary manipulation and various pharmacological agents: nil or temporary.

Details of individual patients, the mode of inheritance, and pathophysiology will be discussed.

#### Long-term prospective follow-up of children with a hiatal hernia (partial thoracic stomach)

I. J. CARRE, R. ASTLEY, AND RHODA LANGMEAD-SMITH (*Department of Child Health, The Queen's University of Belfast, and The Children's Hospital, Birmingham*) It is known that the great majority of infants with vomiting due to a small hiatal hernia (partial thoracic stomach) lose their symptoms spontaneously<sup>1</sup>, a process accelerated by postural treatment, particularly when applied in early infancy<sup>2</sup>. However, despite an absence of symptoms the hiatal hernia can still be identified radiologically in many of these children<sup>3</sup>. The subsequent progress of these asymptomatic children into adult life is as yet unknown. The present study was undertaken to obtain further information on this particular aspect of the disorder.

Eighty-six children with a hiatal hernia (uncomplicated by an oesophageal stricture) who were originally studied by two of the authors (I.J.C. and R.A.) at the Children's Hospital, Birmingham, between 1950-55 have been reviewed by the same two observers. These patients had either received no specific treatment or had been managed conservatively by postural therapy; none had been treated surgically. All were over 20 years old at review. Although over 90% were symptom-free on reassessment, approximately half still had a hiatal hernia demonstrable on fluoroscopic examination. None had developed a stricture.

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#### Is there a myoelectrical abnormality in the irritable colon syndrome?

I. TAYLOR, C. DARBY, P. HAMMOND, AND P. BASU (introduced by Professor R. SHIELDS) (*Departments of Surgery and Bioengineering, Liverpool*) It has been suggested that in the distal colon of patients with the irritable colon syndrome (ICS) an abnormality of the 3 c/m slow wave electrical rhythm exists<sup>1,2</sup>. However, it is not clear if this is related to altered bowel habit itself or whether it is a characteristic feature of the syndrome. We have therefore studied 10 patients referred with ICS and 10 patients suffering from disorders with similar symptoms—for example, chronic pancreatitis, diverticular disease, ulcerative colitis, etc.

Transit times, stool weights, percentage motility, and slow wave electrical activity were measured in each patient. The two groups were well matched for age and sex and patients with similar symptoms in the two groups had similar values for transit time and percentage motility.

In the ICS group 48% of the 3 c/m slow wave were accompanied by 3/m motor waves. This did not occur in the control group.

Thus, in the irritable colon syndrome a high incidence of 3 c/m slow wave activity is recognised in the distal colon. This appears to be specific to this condition, but may well be due to its higher amplitude making recognition easier.

#### References

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#### Similarity of bowel distension characteristics in the irritable colon syndrome and diverticulosis

J. RITCHIE (*From the Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford*) The uncertain relationship of diverticulosis to the irritable colon syndrome (ICS) requires further investigation. Colonic motility studies have been undertaken as previously described<sup>1</sup> on 182 patients (mean age 43 years) with symptoms resembling ICS. In 46 (25%) of these, diverticula were protruded during the study. Other organic disease was excluded. These patients were compared with 22 asymptomatic subjects (mean age 51) of whom seven (32%) were found to have diverticulosis. The predicted proportion for this age was 30%.

ICS patients and those with diverticulosis were each divided into three groups on their response to balloon distension. Patients in group 1 could not tolerate inflation beyond 60 ml. Group 2 felt pain at 60 ml but could be further inflated, and group 3 had no pain under 100 ml. For both clinical divisions of each group mean values were obtained of the minimum balloon volume causing pain and of the corresponding gut wall diameter and tension. Values for the three parameters differed significantly between groups but not, within each group, between ICS and diverticulosis. The values for asymptomatic subjects were not significantly different from those of the equivalent group 3.

These observations reinforce the hypothesis that diverticulosis is a common asymptomatic condition and that patients with symptoms of pain and dysfunction have ICS in addition.

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