The British Society of Gastroenterology

The 39th Annual Meeting of the British Society of Gastroenterology and the 7th Annual Meeting of the British Society for Digestive Endoscopy were held at Edinburgh on 20-23 September 1978 under the Presidencies of Dr W. Sircus, President of the BSG, and Dr M. Atkinson, President of the BSDE. Following a study day on the Wednesday a full scientific programme of 167 papers was presented to the two Societies. The Plenary Session included the Sir Arthur Hurst Lecture given by Professor Dame Sheila Sherlock entitled ‘Untoward hepatic drug reactions’. The abstracts of the 167 papers follow.

Preventing transfer of malignant cells on non-disposable brushes used for cytology

M. R. B. KEIGHLEY, T. MAKURIA, JANET MOORE, AND H. THOMPSON (The General Hospital, Birmingham) The accuracy of diagnosing gastric carcinoma is increased by the use of brush cytology. In our experience, even with non-disposable brushes, false positive cytology is rare. Four patients in this unit were endoscoped with the same brush on one day, none had visual or biopsy evidence of cancer, but malignant cells were seen on brush cytology in all patients. The neoplastic cells were traced to a patient examined on the previous day. The incidence and prevention of malignant cell transfer was investigated.

Cells were recovered from brushes used on a previous endoscopy list in six of 11 occasions. Vigorous cleaning of the brush removed cells from only seven of 12 contaminated brushes. Washing with detergent, hibitane, pyronex, and pancreatin was without effect but autoclaving removed cells in all of eight brushes. Repeated autoclaving (× 50) did not damage the bristles on disposable brushes. The mean number of cells recovered from disposable brushes (6 × 10^4) was less than from non-disposable brushes (1 × 10^9).

We conclude that, because of an increased yield of cells and reduced cost of non-disposable brushes, this practice should be retained provided that brushes are autoclaved after each examination.

References


ENDOSCOPY

Open access GP endoscopy

G. HOLDSTOCK, M. WISEMAN, AND C. LOEHRY (Royal Victoria Hospital, Bournemouth) We report on three years’ experience of a GP direct referral gastroscopy service. In all, there were 1077 GP referrals, compared to 728 hospital ones. There was no significant difference in either the type or duration of symptoms between the two groups, the vast majority having dyspepsia. Fewer of the GP patients had had a trial of antacids than the hospital referrals. Comparing the first year of the service with the third, 265 additional endoscopies were performed but no extra ulcers or cancers were found. The pick-up rate for these two conditions combined fell from 25 to 13%. There was no significant difference between the pathology found in either group. Despite the increase in numbers of GP referrals, there was no reduction in the number of patients referred either from hospital clinics for endoscopy or for barium studies.

All the GPs in the areas were sent questionnaires and all found the service useful. Seventy-five per cent felt that clinic referral was reduced. It is concluded that, although feasible and useful to the GPs, the introduction of the service results in too many patients being referred, and, consequently, there are few objective advantages. Possible ways of limiting the number of patients referred are discussed.

Importance of repeated endoscopy in determining the source of haemorrhage in portal hypertension

K. J. MITCHELL, B. R. D. MACDOUGALL, D. B. A. SILK, AND ROGER WILLIAMS (Liver Unit, King’s College Hospital and Medical School, Denmark Hill, London) Although it is known that patients with portal hypertension and haematemesis commonly develop gastric and duodenal erosions, there is uncertainty as to whether the haemorrhage originates from these or from ruptured varices. To investigate this, two experienced observers performed emergency endoscopy in 76 patients with portal hypertension and oesophageal varices referred for management of haematemesis.

All patients were endoscoped within 24 hours (median four hours) of haematemesis. By this time no evidence of any visible bleeding was found in 54 patients (71%). Spurting or oozing varices were observed in 18 (23.7%). Although superficial erosions were seen in a further 18 patients (23.7%), visible bleeding was observed in only four (5.3%).

Despite cessation of bleeding on initial endoscopy, 35 patients re-bled during the
same admission. Twenty-one were re-endoscoped within six hours (median 0-9 hours). Bleeding from ruptured varices was observed more frequently in this group (71-4%) than at initial endoscopy (23-7%, p> 0.05) and none was found to be bleeding from erosions. Furthermore, two patients previously noted to be bleeding from erosions were bleeding from varices when re-endoscoped.

In two respects these findings differ from those of previous endoscopy series. Firstly, no visible haemorrhage could be identified in most cases on initial endoscopy. Secondly, recurrent haemorrhage was common, and originated from varices and not other sites.

Peptic ulceration in patients with chronic liver disease

A. P. KIRK, R. H. HUNT, J. S. DOOLEY, and SHEILA SHERLOCK (Department of Medicine, Royal Free Hospital, London) Peptic ulceration is said to be more common in chronic liver disease, and often asymptomatic. To assess this, 163 patients with chronic liver disease underwent upper gastrointestinal endoscopy, 106 having dyspeptic symptoms.

Twenty-four peptic ulcers were found (14.7%), 12 were duodenal, eight gastric, and four pre-pyloric. Twenty-two of these 24 patients were symptomatic. Ulcers were found in five of 15 patients with hepatitis B antigen positive chronic liver disease (33%), 10 of 46 with chronic alcoholic liver disease (21.7%), five of 35 with primary biliary cirrhosis (14.3%), two of 19 with miscellaneous liver diseases (10.5%), two of 25 with crypto-genic cirrhosis (8%). Ulcers were not demonstrated in any of 23 patients with hepatitis B negative chronic active hepatitis.

Thirty patients were receiving corticosteroid therapy, five had peptic ulceration, compared with 19 of the remaining 133 patients. The difference was not significant.

Fifty-nine patients presented with gastrointestinal bleeding, but in only four was this due to peptic ulceration.

In conclusion, peptic ulceration occurred in 14.7% of patients with chronic liver disease. It was common in alcoholics and those with hepatitis B surface antigen, but rare in hepatitis B antigen negative chronic active hepatitis. Ulcers were not more frequent in those receiving corticosteroid therapy. The majority of patients with ulcers were symptomatic, and ulcers were rarely the cause of gastrointestinal bleeding.

Reference


Laser photocoagulation for upper gastrointestinal haemorrhage

S. G. BOWN, P. R. SALMON, D. KELLY, B. M. CALDER, AND A. E. READ (Departments of Medicine and Pathology, University of Bristol) Much interest currently centres on therapeutic endoscopy for upper gastrointestinal haemorrhage. The most promising method is laser photocoagulation, but the safety and efficacy have not yet been fully established.

We are currently comparing an Argon with a Neodymium YAG laser in an animal model, and here present the Argon results. Our Spectra-Physics 171 Argon ion laser produces a continuous wave beam of up to 15W. This is transmitted to the bleeding site by a 200 micron single quartz fibre which is enclosed in a 2 mm catheter enabling a coaxial stream of CO2 gas to blow blood away from the lesion. This catheter may be passed down the biopsy channel of a standard endoscope. Our work was performed at open gastroscopy and endoscopically in 10 beagles. Artificial ulcers were created in the stomach of heparinised animals, and the resulting haemorrhage treated with argon laser irradiation of varying total power, power density and duration. The optimum power was 7-9 W, which arrested haemorrhage in 20 out of 21 ulcers. Histological examination showed no thrombosis in acute lesions, whereas chronic experiments showed fibrinoid necrosis in irradiated vessels with delayed healing. Most of the energy was absorbed in the mucosa and submucosa.

New method for endoscopic retrograde cholangiopancreatography (ERCP) in cases of unsuccessful cannulation in jaundiced patients


In five patients with obstructive jaundice of unknown origin traditional ERC failed. Using an Olympus JFB3 duodenoscope small artificial endoscopic choledochoduodenal fistulas by means of a specially designed diathermic cutter (needle type) were performed at the lower end of the intramural portion of the common bile duct in order to achieve ERC. ERC through the endoscopic fistula succeeded with no complications after this procedure in four patients.

In all four a precise diagnosis was made. In one patient the depth of the fistula was not sufficient to reach the CBD lumen and the contrast medium was injected in the duodenal submucosa with the development of a mild fever (38-5°C) with recovery after five days' antibiotic therapy. An attempt to explore the ductal system during surgery (two patients) or at necropsy (two patients) showed no sign of the endoscopic fistula. In one patient with normal bile ducts at ERC, an

The British Society of Gastroenterology
endoscopic control four weeks later showed a normal mucosa at the same site of the fistula.

It is concluded that this method is less invasive and probably safer than PTC in order to carry out cholangiography when ERC fails. Moreover, it may permit an endoscopic choledochoduodenostomy for choledocholithiasis in cases of unsuccessful endoscopic papillosphincterotomy.

Statistical evaluation of the correlation between endoscopic retrograde cholangiopancreatography and pancreozymin secretin test

T. OGURI, T. KASUGAI, AND N. KUNO (introduced by P. R. SALMON) (Aichi Cancer Center Hospital, 1st department of Internal Medicine, Tashirocho, Chikusaku, Nagoya, 464 Japan) Failure of agreement between ERCP and a pancreozymin-secretin test (PS test) may be ascribed to variations in histopathology, differences in the method of ERCP and function testing, accuracy in the performance of the procedures, and the interpretation of the obtained data. As a result, correlations between ERCP and function tests should be analysed statistically. In 1972, the authors proposed criteria for the grading of ERCP in the diagnosis of chronic pancreatitis—that is, minimal, moderate, and advanced stages.

Regressions of total volume, total amylase output, and maximum bicarbonate concentration by PS test were calculated against the grade of ERCP and found to be highly significant (p < 0.001) for all three factors. Regressions of frequency of abnormality below mean value (m) — standard deviation (s) and m—2s in these three factors were highly significant (p < 0.001). The ERCP in those cases in which the ERCP grade did not correlate with PS test showed marked local differences in the grades of pancreatogram. This finding could explain the discrepancy on the assumption that PS test is a functional mean value, whereas ERCP is a structural maximum value.

‘Lassoo’ polypectomy

C. B. WILLIAMS AND P. E. GILLESPIE (St. Mark’s Hospital, City Road, London) Removal of large and broad-based colonic polyps poses a special problem for the colonoscopist as there is a risk of bleeding from the site of resection and perforation of the bowel wall. The endoscopist has had the choice of removing the polyps ‘piecemeal’ in several sessions or of referring patients for abdominal surgery.

Recently we have adapted the method of sigmoid-rectal intussusception, previously described with the rigid proctosigmoidoscope. In our cases, having started conventional snare polypectomy it was considered dangerous to continue; the polyps were ‘lassoed’ using the handleless snare wire which was left in situ tightened onto the base of the polyp, and the colonoscope withdrawn. Under general anaesthesia the polyps were intussuscepted to the anus and locally excised and sutured without difficulty. This intussusception technique should be considered in those with broad-based sigmoid colon polyps judged to be hazardous or impossible to remove by conventional polypectomy.

References


PAEDIATRICS

Duodenal mucosal antibody against bacteria grown from duodenal luminal fluid and mucosa in children with diarrhoea

P. D. MANUEL, V. BANPOE, S. AVIGAD, M. SHINER, AND J. A. WALKER-SMITH. (CRC, Northwick Park, Harrow, Middlesex and the Queen Elizabeth Hospital for Children, Hackney Road, London) Delayed recovery after acute gastroenteritis of infancy remains a major clinical problem. Its cause is unclear, although some cases are due to intolerance to lactose or cow’s milk protein. The role of bacteria, particularly the ‘normal’ gut flora, remains unknown.

We have investigated 29 children under the age of 2 years, 18 with diarrhoea for at least two weeks before study, and 11 without diarrhoea during this period. Bacteria were cultured aerobically and anaerobically from duodenal juice and mucosa taken from these children as part of routine clinical investigation. Using an indirect immunofluorescence technique we have looked for antibody in the duodenal mucosa to bacteria cultured from each patient.

Total bacterial counts were not statistically significantly different between the two groups. Antibody was found in 17 of 18 patients with diarrhoea, but in only two of 10 patients without. The presence of antibody did not depend on an abnormal mucosa, nor on the condition causing the diarrhoea. In a number of patients the antibody has been classed as IgA or IgG or both.

The role of this antibody is unclear; it may mark a changed relationship between these ‘non-pathogenic’ bacteria and the host’s immune system.

Abnormalities of intestinal transport systems in the post-enteritis syndrome (PES) and ‘toddler’ (non-specific) diarrhoea

J. H. TRIPP, J. A. MANNING, D. P. R. MULLER, A. KILBY, J. A. WALKER-SMITH, AND J. T. HARRIES (Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, and Queen Elizabeth Hospital for Children, London) There is now good evidence that some small intestinal secretory states are mediated by alterations in the activities of (Na+/K+)-ATPase and adenylate cyclase (AC) in the mucosal enterocyte. Examples include increased AC activity induced by choleriu and certain other toxins and reduced (Na+/K+)-ATPase in viral diarrhoea, and we have recently demonstrated increased AC and reduced (Na+/K+)-ATPase in active coeliac disease.

We have assayed both enzymes in biopsies obtained from 19 children with PES during the active phase of the disease and from eight during recovery; in four patients sequential studies were performed during and after recovery from PES. Biopsies were also performed in a further group of 23 children with ‘toddler’ diarrhoea (TD).

In the PES patients both enzyme activities were reduced (p < 0.05), and returned to normal or supranormal levels on recovery. In contrast the mean activity of both enzymes was increased in patients with TD (p < 0.05); six of the seven biopsies with raised (Na+/K+)-ATPase activity also had raised AC activity, suggesting the possibility of a linked compensatory process.
Our results suggest that the reduction in both enzyme activities in PES is not simply due to enterocyte immaturity. The similarities between enzyme activities in TD and the recovery phase of PES may indicate that the increased (Na⁺-K⁺)-ATPase activity is a response of normal villous cells to crypt cell secretion.

Liver histology in obstructive jaundice of infancy

R. NELSON, D. SCOTT, AND A. J. WATSON
(Departments of Child Health, and Clinical Pathology, Royal Victoria Infirmary, Newcastle upon Tyne) Liver biopsies obtained during the first few months of life, from 58 children with persistent cholestatic jaundice, were studied retrospectively. Twenty-four histological features were graded 0 to 3, according to the severity of the abnormality, by two pathologists, without knowledge of the clinical details.

Twenty-six patients had extrahepatic bile duct atresia and 32 had 'neonatal hepatitis'. The patients with 'hepatitis', were also grouped according to their clinical progress; 10 died of liver failure in infancy, 15 had recovered normal liver function, and seven had chronic liver disease.

Portal tract expansion, bile duct proliferation, and cirrhosis were features of the liver biopsy in bile duct obstruction, but also in fatal hepatitis. There was no significant difference between obstruction and hepatitis in the incidence of giant cell transformation, pseudo-acini formation, the severity and type of inflammatory cell infiltration, or the presence of piecemeal necrosis, and these features were not helpful in predicting the prognosis of infants with hepatitis; 92% of patients with obstruction, but only 61% with 'hepatitis' were correctly diagnosed by examination of the liver biopsy. 'Hepatitis' patients with poor prognosis were more frequently misdiagnosed as obstruction.

Percutaneous cholangiography in prolonged jaundice of childhood

EDWARD R. HOWARD AND HEATHER B. NUNNERLEY (King's College Hospital, Denmark Hill, London) The radiological demonstration of undilated intrahepatic bile ducts was made easier by the introduction of the Chiba fine needle (Okuda et al., 1974). The needle has now been modified for the investigation of paediatric patients with prolonged jaundice by reducing the external diameter to 0.5 mm and by reducing its length.

Percutaneous transhepatic cholangiography was performed on 22 jaundiced children in whom screening tests suggested surgically correctable lesions in the biliary tract.

In the preoperative investigation of 12 infants with extrahepatic biliary atresia isolated segments of bile ducts, dilated extrahepatic lymphatics and normal hepatic veins were seen. Postoperative cholangiograms in two patients with atresia were successful in demonstrating a patent bile duct anastomosis in one case and portal hypertension in the other.

Patent biliary tracts were visualised in cases of hepatitis syndrome and hepatic fibrosis and in consequence surgery was avoided in two infants. Three children with intrahepatic biliary hypoplasia were also investigated.

The anatomy of the extrahepatic ducts was clearly demonstrated in three older children who had lesions of the common bile duct.

Percutaneous cholangiography with the very fine needle has been free of complications in these young patients and the investigation has contributed to both the diagnosis and surgical management of their jaundice.

Effect of serum from patients with pancreatic insufficiency (PI) on jejunal transport in the rat jejunum in vivo

G. BANCHINI, J. H. TRIPP, E. ROMA, P. J. MILLA, D. P. R. MULLER, AND J. T. HARRIES (The Hospital for Sick Children, Great Ormond Street, and Institute of Child Health, Guilford Street, London) Araki et al. demonstrated that cystic fibrosis (CF) serum inhibited glucose-stimulated short circuit current in rat jejunum in vitro, and suggested that this was a specific phenomenon reflecting a CF 'factor'. Subsequently we showed that CF serum inhibited glucose transport in rat jejunum in vivo. In this study we compare the effects of serum from children with CF, Shwachman's syndrome (SS), and protracted diarrhoea (PD) without PI on jejunal transport in the rat jejunum in vivo using a closed-loop technique. Compared with control serum, CF serum inhibited net absorption of glucose (P < 0.001), sodium (P < 0.01) and water (P < 0.05). Glucose absorption was not inhibited by heterozygote serum. SS serum behaved in a similar way to CF serum, inhibiting glucose (P < 0.05) and water (P < 0.05) absorption. In contrast, PD serum had no effect on glucose absorption.

These results indicate that the inhibitory effects of CF serum are not specific, and occur in other types of PI. We suggest that either (1) a 'factor' is present in normal serum, and is presumably secreted by the pancreas, which enhances absorption of glucose, water, and sodium, or (2) an inhibitory 'factor' is present in PI serum.

References


Diagnosis of childhood Crohn's disease: value of colonoscopy

C. A. CAMPBELL, C. B. WILLIAMS, AND J. A. WALKER-SMITH (Department of Gastroenterology and Child Health, St. Bartholomew's Hospital) Crohn's disease is being increasingly diagnosed in the paediatric age group; we have seen 13 cases between the ages of 6 and 15 years in this department in the last two years. The diagnosis was ultimately made on radiological or pathological grounds.

There was often a prolonged delay between onset of symptoms and diagnosis because of lack of awareness of the disease in childhood, the vague symptom pattern, and inconclusive initial investigations. 1

We now perform early total colonoscopy in suspected cases under sedation, without general anaesthesia, using the adult colonoscope.

Small aphthoid ulcers can easily be seen in the colon and terminal ileum even at a stage when they are radiologically undetectable. Such appearances are recorded by conventional and polariod photographs and videotape; they are
characteristic of Crohn's disease, although the small biopsy specimens infrequently show diagnostic granulomata.

Colonoscopy is a simple, practical, and rewarding procedure as an early investigation in any child in whom there is a possibility of Crohn's disease.

Reference

GI HORMONES

Cellular localisation of gastrin in the human small intestine

A. M. J. BUCHAN AND J. M. POLAK (Department of Histochemistry, RPMS, Ham-merSmith Hospital, London) Two major forms of gastrin, little G17 and big G34, are extracted from antral and upper small intestinal mucosa. The origin of both peptides in antral mucosa was established as the ultrastructurally defined G cell. G cells contain secretory granules, ranging from small (200 nm) and electron dense to large (400 nm) and electron lucent. Although ultrastructurally identifiable G cells are present in the Brunner's glands, therefore are absent in intestinal mucosa. Therefore the cellular origin of intestinal gastrin remained undetermined.

We present here data gathered from the investigation of 30 samples of duodenum and jejunum on the identification of the intestinal gastrin-producing cell. We used three region specific antisera to immunocytochemically identify the cells by the semithin/thin method.

Antisera 1295 (specific for G17) and L33 (specific for G34) stain a totally distinct endocrine cell population from the CCK specific antiserum (Z58). The gastrin-containing cells have small (190 nm) electron dense secretory granules compared to the large I cell granules (250 nm) containing CCK. These cells were probably included in the D1 cell category in previous classifications. We suggest the name SIG for these small intestinal gastrin-containing cells in order to distinguish them from other small granulated cells found in the intestine.

Raised motilin in diarrhoea

S. R. BLOOM, N. D. CHRISTOFIDES, AND H. S. BESTERMAN (Department of Medicine, Royal Postgraduate Medical School, London) Motilin, a newly discovered hormone from the upper intestine, has powerful pharmacological actions on gut motor functions. It greatly accelerates postprandial gastric emptying and can induce the formation of interdigestive myoelectric complexes. In order to determine if it might play a role in the abnormal motility associated with diarrhoeal states, fasting motilin concentrations were measured in several different groups of patients with active diarrhoea.

Plasma motilin was determined by a radioimmunoassay which was capable of detecting changes of 3 pmol/l and showed no cross-reaction with other gut hormones. In 16 healthy controls the mean fasting level was 56 ± 8 (SEM) pmol/l. In eight patients with diarrhoea due to severe tropical sprue, the motilin concentration was 142 ± 16 pmol/l, in 12 patients with acute infective diarrhoea it was 140 ± 26 pmol/l, in 13 patients with Crohn's disease it was 202 ± 55 pmol/l, and in 12 ulcerative colitis patients it was 150 ± 41 pmol/l (all P < 0.01 against controls using Wilcoxon sum of ranks test). In contrast, 11 patients with constipation had normal levels of 55 ± 9 pmol/l. Thus, motilin is significantly raised in diarrhoea states and may well play a significant role in the upper gastrointestinal motor changes associated with diarrhoea.

References

VIPergic innervation of the human pancreas

A. E. BISHOP, J. M. POLAK, M. G. BRYANT, AND S. R. BLOOM (Departments of Histochemistry and Medicine, RPMS, Hammer-Smith Hospital, London) Vasoactive intestinal polypeptide (VIP) has a variety of effects on the exocrine and endocrine pancreases. These include the stimulation of bicarbonate secretion and alkaline juice flow, and the release of glucagon, pancreatic polypeptide, and insulin.

As VIP is rapidly cleared from the circulation, it is unlikely that it normally acts as a circulating hormone. VIP probably functions as a local tissue hormone or neurotransmitter. This suggests that the powerful effects of VIP on the pancreas may be mediated by a source of VIP within the pancreas. This possibility was investigated by a morphological and quantitative study carried out by the combined techniques of immunocytochemistry and radioimmunoassay.

Radioimmunoassay showed that VIP can be extracted from the human pancreas in amounts averaging 33 ± 9 pmol/g. Immunocytochemistry localised this VIP content in fine, varicose nerve fibres. The fibres ran through the connective tissue and the exocrine pancreas. They could also be seen in close contact with the pancreatic islets.

The finding of the presence of VIP can, therefore, help in the interpretation of many physiological and pathological responses of the exocrine and endocrine pancreas. Further functional studies are needed to demonstrate the exact role of the VIPergic fibres in the pancreas.

'Big' cholecystokinin?: evidence for existence in human serum

C. E. MARSHALL, S. L. HOWELL, AND A. G. JOHNSON (Professorial Department of Surgery, Charing Cross Hospital Medical School, London) Experiments were performed to investigate the possible existence of multiple molecular weight forms of biologically active cholecystokinin in human serum. Serum samples were fractionated on Sephadex columns using Krebs' solution as the eluting buffer. Eluates from the columns were fed directly into a modification of the superfusion system for bioassay of cholecystokinin activity with rabbit gall-bladder strips already described.1,2,3 By splitting the stream the analysis was performed in duplicate. Columns were calibrated with Boots pancreozymin, octapeptide of cholecystokinin, and 99% pure cholecystokinin. Under these conditions, on application of sera, two distinct peaks of cholecystokinin activity were eluted from G50 columns; the first corresponded to a large molecular weight molecule eluted with the void volume, the second to 33 amino acid cholecystokinin, although these columns did not separate the full cholecystokinin molecule from its octapeptide. Analysis of the sera from subjects fasting and after a standard fatty meal indicates that it is the low molecular weight component that is released after a stimulus, the high molecular weight

Raised motilin in diarrhoea

5*
These experiments suggest the presence of an active uptake process for circulating serum trypsin which is then resecreted into the duodenum.

Reference

Urine trypsin concentration in the diagnosis of pancreatic disease

G. LAKE-BKAAR AND J. A. SUMMERFIELD (introduced by PROFESSOR DAME SHEILA SHERLOCK) (Department of Medicine, Royal Free Hospital, Pond Street, London) A radioimmunoassay (RIA) for the measurement of serum trypsin concentration has recently been described. In general, high fasting serum levels are found in cancer of the pancreas and low levels in chronic pancreatitis, but there is considerable overlap between the groups.

In this study the fasting early morning urine trypsin concentration in 38 subjects was estimated by RIA. Each specimen was concentrated using a microconcentrator. Urine trypsin concentration (μmol/ml) was measured by the Jaffe reaction.

In 13 healthy volunteers, a mean urine trypsin concentration of 1.02 ± 3.4 ng/ml (mean ± SEM) was obtained. In three patients with chronic renal failure and six with acute pancreatitis, mean urine trypsin concentrations of 28 ± 23 ng/ml and 7.5 ± 4.3 ng/ml respectively were found.

In nine patients with chronic pancreatitis a mean urine trypsin concentration of 0.3 ± 0.2 ng/ml was obtained. However, in seven patients with cancer of the pancreas, the mean concentrations was 10.3 ± 4.5 ng/ml. This was significantly different from the chronic pancreatitis group (t = 2.74, p < 0.01).

The ratio of the trypsin concentration to the creatinine concentration in the urine yielded a similar pattern of results.

We conclude that in the differential diagnosis between chronic pancreatitis and cancer of the pancreas, a single urine trypsin determination in a fasting early morning specimen may prove useful.

Reference

Hypotrypsinaemia in diabetes mellitus

T. E. ADRIAN, A. J. BARNES, AND S. R. BLOOM

The British Society of Gastroenterology

(continues)
hypocalcaemia. We have investigated 21 patients with very severe acute pancreatitis (at least four objective prognostic factors present). Sequential monitoring of plasma PTH levels was performed during the first week of hospitalisation and correlated with hypocalcaemia and outcome of disease. All eight patients with severe hypocalcaemia (corrected calcium < 2.0 mmol/l) had associated rises of plasma PTH levels (normal up to 600 ng/l). The mean of the maximal PTH in these patients was 1183 ng/l (range 660-1700) and these high levels were usually recorded within the initial 36 hours. Thereafter a gradual decrease in plasma PTH occurred, accompanied by a restoration of serum corrected calcium within the normal range (2.2-2.6 mmol/l).

The mortality in this group of patients was 33%, and six of the seven who died exhibited significant rises of PTH, the exception being a death associated with recurrent myocardial infarction and normocalcaemia. This study indicates an adequate PTH response to be present in the most severe pancreatitis.

References

Screening for pancreatic disease: comparison of grey-scale ultrasonography and isotope scanning

J. M. Rhodes, J. A. Agnew, J. A. Summerfield, E. Elias, R. A. Horrocks, P. M. Chudleigh, and L. A. Berger (Royal Free Hospital, Pond Street, London) There is still no clearly established screening test for pancreatic disease. The rationale for ultrasonography generally gives few false-positives but many false-negatives.1 Grey-scale ultrasonography, while promising,2 has not yet been adequately compared with isotope scanning.

Both isotope and ultrasound scans were performed prospectively in 40 patients with suspected pancreatic disease. The diagnosis was established by laparotomy (23), endoscopic pancreateography (nine) or clinical follow-up for at least nine months (eight). All 13 patients with pancreatic carcinoma had abnormal isotope scans and only one had a normal ultrasound scan. The eight patients with chronic pancreatitis all had abnormal ultrasound and isotope scans. However, of 19 normal patients, 12 had abnormal isotope scans compared with only three false-positive ultrasound scans.

A review of isotope scanning in the Royal Free Hospital since 1973 (n = 314) and ultrasound scanning during 1977 (n = 115) yielded similar results. In pancreatic carcinoma ultrasound was falsely-normal in 1/22 (5%), isotope scanning falsely-normal in 2/92 (2%). In chronic pancreatitis the false-negative rate for ultrasound was 1/15 (7%), for isotope 10/88 (11%). However, in normal patients, ultrasound yielded only 12/78 (16%) false-positive scans in contrast to isotope scanning with 64/134 (48%) false-positives.

In conclusion, ultrasound scanning of the pancreas has a false-negative rate similar to isotope scanning but a much lower false-positive rate. It should now be the screening test of choice for pancreatic disease.

References

Postprandial secretin stimulates pancreatic bicarbonate secretion in man

G. R. Greenberg, S. Domschke, M. G. Bryant, W. Domschke, W. Roeth, and S. R. Bloom (Royal Postgraduate Medical School, London, and University of Erlangen, Nurnberg, Erlangen, Germany) We have recently reported that in man a rise in plasma secretin of 3-5 pmol/l is observed during both endogenous acid stimulation (pentagastrin) and after a meal. Whether such low levels are sufficient to stimulate pancreatic bicarbonate has not, however, been determined. Pure pancreatic juice was collected after direct cannulation of the main pancreatic duct (n = 6) during intravenous GII secretion (0.03 CU kg⁻¹ h⁻¹). Because potentiation may occur with cholecystokinin, the addition of caerulein (15 ng kg⁻¹ h⁻¹) was also studied.

During secretin, bicarbonate output increased from basal levels of 27 ± 12 μEq/5 min (mean ± SEM) to 182 ± 24 (p < 0.001). Addition of caerulein resulted in a further significant increase to 396 ± 50. Plasma secretin increased to 2.1 pmol/l during the infusion and was not affected by caerulein. The similarity of porcine to human secretin was suggested by gel chromatography studies of postprandial human plasma, where one peak eluted in an identical position to both porcine secretin and to human duodenal tissue.

These studies demonstrate that plasma levels of secretin after a meal, though small, are sufficient to stimulate pancreatic bicarbonate and support the hypothesis that secretin has a physiological role in man.

O-14-D-O breath test of the fat digestive capacity of the pancreas

Y. Ghoos, G. Vantrappen, P. Rutgeerts, and P. Schurbmans (Department of Medical Research, University of Leuven, B-3000 Leuven, Belgium) The rationale of this new test is the fact that hydrolysis of the triglyceride O-14-D-O (1,3 dioleyl, 2-14C decanoyl glycerol, synthesised by G. Koch, Unilever) results in a labelled medium chain monoglyceride or fatty acid which is readily absorbed and metabolised to CO₂. 5 μCi O-14-D-O is taken with lunch and breath CO₂ is trapped in 2 mmol hyamine hydroxide before and 1, 2, 3, 4, 5, 6, 8, 10, 20 and 24 h after lunch. The amount of CO₂ is expressed as the 10 h cumulative percentage of the administered dose. Twenty-five normal subjects, 12 proven chronic pancreatitis, eight pancreatectomy, 12 gluten enteropathy, and eight bile acid deficient patients were studied. Results: (1) All pancreatic patients, even those without steatorrhoea, had 14CO₂ excretions (6%-50%) well below the normal range (54%-90-50%); (2) pancreatic enzyme treatment increased 14CO₂ excretion in eight of 10 pancreatic patients studied (mean increase: 23%); (3) the 14CO₂ excretion in patients with steatorrhoea due to bile acid deficiency was 25% higher than in patients with pancreatic steatorrhoea; (4) 14CO₂ excretion was low in seven of 12 gluten enteropathies. Submaximal CCK stimulation normalised the test in the two patients studied. The data suggest that the O-14-D-O breath test is a sensitive and specific test of fat digestive capacity of the pancreas.

Physiological plasma levels of pancreatic polypeptide (PP) inhibit stimulated pancreatic and biliary secretion in man

G. R. Greenberg, R. F. McCloy, T. E. Adrian, V. S. Chadwick, J. H. Baron, and S. R. Bloom (Royal Postgraduate
A physiological role for PP in man is not established, yet mean concentrations in plasma of 250 pmol/l are observed after a meal. Although pharmacological doses of PP inhibit pancreatic secretion in the dog, it is not known in man whether a similar effect occurs at these post-prandial plasma concentrations. Therefore, using a duodenal perfusion technique to measure pancreatic and biliary outputs, we infused bovine PP (60 pmol kg⁻¹ h⁻¹) in seven healthy subjects during stimulation with GHH secretin (0-1 CU kg⁻¹ h⁻¹) and caerulein (10 ng kg⁻¹ h⁻¹) closely to approximate physiological conditions.

Mean stimulated trypsin output of 20-4 ± SEM 0-3 KU h⁻¹ was reduced to 8.3 ± 0.2 (p < 0.001) during PP. A significant 80% reduction in bilirubin output was also observed. After PP both parameters recovered to preinfusion levels. In contrast, mean bicarbonate output of 20 ± 4 mmol h⁻¹ was unaffected by PP. Incremental plasma PP levels of 250 ± 23 pmol/l during the infusion are equivalent to those after a meal.

We conclude that, in man, PP inhibits stimulated trypsin and bilirubin outputs at plasma concentrations which are observed physiologically. These effects, which are in direct opposition to actions of cholecystokinin, suggest PP may have a role in the regulation of post-prandial pancreatic enzyme secretion and gall bladder storage.

**Peroperative transduodenal pancreatic biopsy**

D. E. E. Tweedle (University Hospital of South Manchester) Peroperative pancreatic biopsy can provide valuable information but has been associated with major complications (particularly fistulae) and a mortality of 3-8%. Peroperative transduodenal biopsy has been attempted in 65 patients since 1972 using the disposable Trucut needle (Baxter-Travenol) and pancreatic tissue was obtained in 62. In 28 cases the preoperative diagnosis of malignancy was confirmed by biopsy in 23 and, of the remaining five patients, three had malignancy. In six cases the preoperative diagnosis of chronic pancreatitis was confirmed by biopsy in five and there was one unsuspected malignancy revealed by biopsy. In 28 cases with a preoperative diagnosis of acute or acute relapsing pancreatitis, inflammation was observed in five, normal tissue in 22, and unsuspected malignancy in one case.

The procedure produced a suberosal haematoma in three patients but this did not complicate the postoperative course. Acute pancreatitis, fistulae, pseudocyst, and subphrenic abscess did not occur.

Peroperative transduodenal biopsy is a relatively safe method of providing a histological diagnosis in disease of the head of the pancreas, and may reveal unsuspected malignancy.

**Cancer of the pancreas and extrapancreatic biliary apparatus—a study of its behaviour in 150 patients**

R. M. Rainbury, Lord Smith, and J. C. Gazet (Gastrointestinal Unit, St. George's Hospital, London). A consecutive series of 150 patients with carcinoma of the pancreas or extrapancreatic biliary apparatus have been reviewed and reclassified according to a proposed (S)TNM(P) classification based on surgical exploration. Results of surgery have been related to multiple parameters, including presenting symptoms and time, sex, age, delay in diagnosis, type of surgery, and subsequent care with (S)TNM(P). Whereas there was a close correlation in all tumours between tumour size and survival, there was no consistent relationship between tumour differentiation, or nodal involvement and survival in any group. But the ideal tumour—that is TNM(P) 1001 or 1002—did not necessarily do best, as four out of five survived less than 300 days (182, 203, 206, 281, and 1234).

But radical resection in carefully selected patients was the most effective treatment and biliary bypass alone was associated with longer survival than when combined with gut bypass or when gut bypass alone was performed. However, in all other groups and in all tumour sites, those treated subsequently with chemotherapy (59) survived longer with a mean of 359 days, than those not (29) who survived an average of 286 days.

**Aspiration cytology of the pancreas at ERCP**

R. A. Mountford, P. R. Salmon, J. Lever, P. Brown, S. G. Bown, and A. E. Read (University Departments of Medicine and Pathology, Bristol Royal Infirmary, Bristol) Patients with suspected pancreatic carcinoma, supported by ERCP, were subjected to percutaneous aspiration cytology using a Chiba needle. Lesions of the head were approached using a posterior approach, lesions of the body from the front. Three types of pancreateographic appearance were selected as suitable:

1. Minor narrowing of the main pancreatic duct. In this circumstance the catheter was maintained in position, with the patient prone, so that contrast was retained in the duct system. Fluoroscopy was employed to guide the needle along the axis of the x-ray beam.

2. Major narrowing of the pancreatic duct. In these cases contrast remained within the duct, allowing the duodenoscope to be removed, so that the needle tip could be positioned by parallax.

3. Complete occlusion of the juxtapapillary pancreatic duct. The biliary tree was opacified and aspiration performed medial to the common bile duct, again rotating the patient.

In 15 attempted aspirations, pancreatic cells were identified in 11 cases (73%), and carcinoma confirmed in four cases. No complications were encountered.

The technique provides a tissue diagnosis, and illustrates the importance of a multi-disciplinary approach to the diagnosis of pancreatic cancer.

**Gastroenteral lesions in Crohn’s disease**

G. Wyndham Stevenson (Department of Pathology, McMaster University Medical Centre, Ontario, Canada) Results of double contrast barium meal from 87 patients with ileal and/or colonic Crohn’s disease, and 88 patients without Crohn’s disease have been reviewed. Superficial gastric and duodenal erosions, thickened and abnormal antral and duodenal folds, and duodenal strictures were found more frequently in patients with Crohn’s disease but occurred in those without. Certain combinations of these abnormalities, however, were strongly suggestive of Crohn’s disease, particularly in the younger age group. Endoscopy confirmed the validity of the radiological diagnoses of superficial gastric and duodenal erosions, and showed that, where thickened abnormal antral and duodenal
folds were present on radiographs, additional superficial erosions were frequently seen at endoscopy. Where erosions were detected endoscopically, they were demonstrated on radiographs in 50% of the patients. Endoscopic biopsies were taken in five patients with both gastric and duodenal erosions, and histological lesions of Crohn's disease found in four. Double contrast barium meals showed combinations of abnormalities strongly suggestive of gastro-duodenal Crohn's disease in 18 patients (21%). The radiological and endoscopic features of gastroduodenal Crohn's disease will be illustrated.

Lymphocytotoxic antibodies in Crohn's disease

A. S. PEÑA I. T. WETERMAN, G. KUIPER, M. C. CASTELLI, A. VAN LEEUWEN, AND J. J. VAN ROOD (Department of Gastroenterology and Department of Immunohaematology, Leiden University Medical Center, The Netherlands) We have investigated the presence of lymphocytotoxic antibodies in the sera of 119 unrelated patients with Crohn's disease with two different techniques, the microcytotoxicity assay of Ting et al. (1973) and the two colour fluorescence technique (TCF) of van Rood et al. 1976. As controls we have screened with the same techniques 119 sera from healthy donors matched for sex and age. Patients and controls were screened against a panel of at least 29 cells with different and well defined HLA specificities.

We have found that the TCF technique is much more sensitive to detect lymphocytotoxic antibodies than Ting et al.'s technique.

In the TCF 84% of patients with Crohn's disease had antibodies directed against B cells as opposed to 6% of the healthy controls. Sixty-six per cent of Crohn's patients had antibodies against T cells as opposed to 3% of the healthy controls. Several of the positive patients had not received previous blood transfusions and/or had been pregnant. Most antibodies were not directed against well defined HLA specificities.

These findings confirm and extend the findings of Korsmeyer et al. using a different technique and a different patient population.

References


Lysosomal enzymes in monocytes and in sera of patients with inflammatory bowel disease

A. S. MEE AND D. P. JEWELL (Academic Department of Medicine, Royal Free Hospital, London) Granulomata are largely composed of macrophages derived from circulating monocytes. The activity of peripheral blood monocytes has therefore been assessed in 21 patients with Crohn's disease (CD), 19 patients with ulcerative colitis (UC), and 21 healthy controls by assaying the activity of the lysosomal enzyme N-acetyl-

β-D-glucosaminidase. Monocytes were isolated from heparinised blood by density gradient centrifugation followed by glass adherence, resulting in 80-90% viable monocytes. Monocyte enzyme activity (±SEM) in CD patients was 4.54 ± 0.28 n mol/10^4 cells/h, 4.99 ± 0.46 in UC patients and 3.09 ± 0.09 in the normal controls (CD v N, p < 0.01; UC v N, p < 0.01). There was a positive correlation between enzyme activity and disease severity for patients with UC (p < 0.01) and a similar trend was seen for patients with CD, although this did not reach statistical significance.

Enzyme activity was also measured in sera from 34 patients with CD, 27 patients with UC, and 39 controls. Serum enzyme activity was significantly increased in patients with both diseases (p < 0.01) but there was no correlation with disease severity.

No difference was observed in either monocyte or serum enzyme activity between patients with CD and those with UC.

The results show that monocytes are activated in inflammatory bowel disease. Raised serum levels suggest that the release of lysosomal enzymes from cells, including monocytes, may contribute to tissue damage in both diseases.

Controlled trial of disodium cromoglycate as maintenance therapy for ulcerative colitis

C. P. WILLOUGHBY, M. F. HEYWORTH, J. PIRES, AND S. C. TRUELOVE (Nuffield Department of Clinical Medicine, Radcliffe Infirmary, and Department of Morbid Anatomy, Radcliffe Infirmary, Oxford) There is evidence that disodium cromoglycate (DSCG) is of some value in the treatment of ulcerative colitis.1,2 The present study was designed to compare its efficacy in the prevention of relapse with that of sulphasalazine (SASP) and with that of the two agents used in combination. The trial period lasted for six months and doses used were 800 mg DSCG daily (the manufacturers recommended dose) and 2-0 g ASP daily.

One hundred and twenty patients with ulcerative colitis were admitted to the trial and assigned at random to the three types of treatment. A relapse was defined as the recurrence of colitic symptoms accompanied by sigmoidoscopic and biopsy evidence of inflammation. The interim results show that the patients on DSCG were four times as likely to suffer a relapse as those on ASP or on the two treatments combined.

We conclude that, in the dose used, DSCG is an ineffective maintenance treatment for ulcerative colitis and that no benefit is obtained by combining it with a standard dose of ASP.

References


Double-blind controlled trial of disodium cromoglycate (DSCG) in the treatment of Crohn's disease

M. J. GRUNDMAN, S. E. WILLIAMS, AND L. A. TURNBERG (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) Disodium cromoglycate has been shown to be of some value in the treatment of ulcerative colitis1 and proctitis2 in limited numbers of cases. The present trial was performed to assess the value of this treatment in Crohn's disease.

Twenty-three ambulant outpatients were randomly allocated for six months treatment with DSCG (1200 mg/day) or placebo in addition to their regular therapy. Patients were crossed over to
The alternative treatment after six months. Monthly assessments were made of symptoms, signs, haematological and biochemical tests. Sigmoidoscopy and rectal biopsies were performed three-monthly. All data were analysed by computer for comparison of individual indicators of activity and of a calculated Crohn's Disease Activity Index. Six patients failed to complete the trial for a variety of reasons. No significant side-effects were noted. No difference was found between active treatment and placebo periods for the Activity Index or for any symptom, sign, or laboratory result. Neither the site nor the extent of the disease had any influence on these findings.

We conclude that DSCG, given for six months, is of no benefit in the treatment of patients with Crohn's disease.

References


LIVER AND BILARY/Clinical Diagnosis

Is raised plasma oestrone in cirrhotic men just an incidental finding?

J. R. B. Green, H. L. Goble, C. R. W. Edwards, A. M. Dawson (Department of Gastroenterology, St. Bartholomew’s Hospital, London) Failure by the diseased liver to inactivate endogenously produced oestrogens is the traditional explanation for the feminising changes seen in some cirrhotic men. Recent studies in these men, however, have shown increased plasma concentrations of oestrone rather than of the more biologically potent oestradiol. As oestrone is considered a weak oestrogen with little biological activity, the significance, if any, of increased plasma oestrone in feminised cirrhotic men is not clear.

To assess possible pathogenetic significance of increased plasma oestrone in cirrhotic men, oestrone was infused into eight men without hepatic disease to produce plasma oestrone concentrations similar to those found in cirrhotic men without altering other plasma oestrogens. In controlled experiments, gonadotrophic-releasing hormone (Gn-RH) was given both by bolus injection and separately by slow infusion. The effect of high plasma oestrone concentrations on the stimulated pituitary release of gonadotrophins was measured.

The results of the study show that high plasma oestrone concentrations significantly impair pituitary responsiveness to a slow infusion of Gn-RH, although not to a single intravenous bolus.

This study clearly shows for the first time that raised plasma oestrone in cirrhotic men could well exert important pathogenetic effects and it suggests that oestrone may not be just an inert metabolite of little significance in these patients.

Liver lipid and liver function after small intestinal resection and two types of jejunooileal bypass in rats

R. Mccourian, K. R. P. Rutter, L. Ang, H. Cleeve, and J. D. Maxwell (St. George’s Hospital Medical School, London) Fatty liver and hepatocellular failure, the most serious complications of intestinal bypass surgery, has been attributed to intestinal bacterial overgrowth and consequent bacterial metabolism of ingested nutrients to hepatotoxic metabolites.

We therefore compared liver function and lipid concentrations in rats with:

1. 90% small intestinal resection (group R);
2. 90% jejunooileal bypass (group B);
3. 90% jejunooileal bypass, with the excluded segment disconnected from functioning gut and exteriorised (group E).

All groups lost 20% of body weight after two weeks. Thereafter (R) increased to 90% of initial weight. However B and E failed to regain, and by 10 weeks were 65-70% initial weight (p < 0.01).

Liver function in R did not differ from controls, but B and E had threefold rises in plasma alanine-aminotransferase (p < 0.02) and aspartate-aminotransferase (p < 0.05), and lower plasma albumin. Hepatic triglyceride increased in all three groups (control: 7.0 ± SD 1.6 mg/g; R: 14.3 ± SD 10.3 mg/g, p < 0.01; B: 15.0 ± SD 8.8 mg/g, p < 0.01; E: 13.4 ± SD 16.0, p < 0.001). Hepatic cholesterol was unchanged.

Thus hepatic dysfunction associated with a long bypassed segment of small bowel is (1) independent of hepatic lipid accumulation, and (2) occurs whether or not the segment is in continuity with functioning gut.

These findings do not support the view that intestinal bacterial metabolism of ingested nutrients contributes to hepatic disease after jejunoileal bypass surgery.

Cell-mediated immunity to a liver specific antigen in patients with cystic fibrosis and liver disease

G. Miel, H. T. Psacharopoulos, A. Nicholson, A. L. W. F. Eddleston, A. P. Mowat, and R. Williams (Liver Unit and Department of Child Health, King's College Hospital and Medical School, Denmark Hill, London) Improved management of pulmonary and pancreatic complications of cystic fibrosis allows 80% of children to survive to adult life, but in 10% significant liver disease then develops. We have studied the relationship between cell-mediated immune responses to liver antigens and the development of liver damage.

Inhibition of leucocyte migration by purified liver specific lipoprotein (LSP), derived from hepatocyte plasma membrane, was shown in nine of 11 children with cystic fibrosis and liver disease but in only five of 14 with cystic fibrosis and no overt liver disease (p > 0.025). Of 12 normal children only one had a slightly reduced migration index.

Lymphocyte cytotoxicity to isolated rabbit hepatocytes was significantly increased in 10 of 13 children with cystic fibrosis and liver disease, but in only six of 29 cases of cystic fibrosis without liver disease (p > 0.001). Experiments using lymphocyte subpopulations showed that the cytotoxicity was mediated by a non-T cell population and could be blocked with LSP in seven of 10 cases, suggesting that the reaction in these patients was specifically directed against LSP.

The study demonstrates an association between potentially damaging immune responses to liver antigens and the presence of clinically evident liver disease in patients with cystic fibrosis.

Functional activity of the alternative complement pathway in chronic liver disease

L. E. Munoz, K. Titisikas, H. C. Thomas, and S. Sherlock (Department of Medicine, The Royal Free Hospital, London) Immune complexes (IC) are associated with increased catabolism in patients with HBsAg positive chronic active
liver disease (CALD) and primary biliary cirrhosis (PBC), but not in HBsAg negative CALD and alcohol-induced liver disease (ALD).

To determine whether failure of IC to activate C3 is due to diminished alternate pathway amplification function, we examined the percentage conversion of C3 to C3b by a standardised activant of this pathway (Saccharomyces cerevisae yeast) and the ability of these sera to support phagocytosis of this yeast by normal polymorphs (alternative pathway dependent function).1

The percentage conversion of C3 to C3b in 12 normal subjects was 50.5% ± 11.8 (M ± SD). Normal values were obtained in PBC (48.7% ± 9.4) and HBsAg positive CALD (45.1% ± 17.8) but significantly reduced levels occurred in HBsAg negative CALD (36.6% ± 7) (p < 0.001) and ALD (31% ± 9-6) (p < 0.01).

The opsonic capacity of these sera was increased or normal in PBC, HBsAg positive and negative CALD and decreased in ALD.

To summarise, the functional activity of the alternate pathway of complement is reduced in ALD and to a lesser extent in HBsAg negative CALD. It is normal in HBsAg positive CALD and PBC. This reduced activity may explain why in HBsAg -ve CALD and ALD IC do not result in increased activities of C3, the biologically important component of complement.

Reference


Chronic active hepatitis in the United Kingdom and Iraq

G. HOLDSTOCK, S. RASSAM, J. G. C. KINGHAM, H. M. SADLER, AND R. WRIGHT (Southampton University Hospitals and Department of Medicine, Medical City, Iraq) The clinical, immunological, and biochemical features of biopsy-documented chronic active hepatitis have been compared in 26 patients from the United Kingdom and 40 patients from Iraq. Immunological studies were undertaken in one laboratory (Southampton) and included HBV markers, autoantibodies and DNA-binding antibodies. United Kingdom patients had a low incidence of HBsAg (8%) compared with Iraqis (83%). They were more likely to be female and have an onset with jaundice.

They had a high incidence of other putative autoimmune diseases and autoantibodies, with the exception of DNA-binding antibodies, and higher globulin levels. Anticore antibodies were only rarely detected in HBsAg-negative patients from both countries (less than 4%).

Iraqi patients were more likely to present with fluid retention and abdominal pain and had lower albumin levels and less pronounced rises in the serum transaminases. Only one patient from Iraq had clinical and immunological features of a 'lipoid' hepatitis.

This suggests that HBsAg positive and negative chronic active hepatitis are aetologically distinct and that there is a striking geographical variation in their prevalence.

Hepatitis Bs antibody in chronic liver disease

P. R. MILLS, T. H. PENNINGTON, R. N. M. MACSWEEN, AND G. WATKINSON (Departments of Medicine, Virology and Pathology, Western Infirmary, Glasgow) The hepatitis B surface antibody (anti-HBs) is found commonly in sera from healthy communities as an indicator of previous subclinical hepatitis infection. We have conducted a prospective survey of antibody carrier rate among 160 patients with histologically-proven chronic liver disease and 28 chronic alcoholics without liver disease. Anti HBs was assayed by Abbot Ausab radioimmunoassay kit on coded sera and recorded as positive or negative. All patients sera were HBsAg negative.

There was a striking increase in the antibody carrier rate in patients with alcoholic cirrhosis (7/28—25%) (p < 0.05) and alcoholic cirrhosis with portal hypertension (12/23—52%) (p < 0.001) when compared with a control population of 161 hospital patients without liver disease (14/161—8.7%) who were age and sex-matched with the patients with alcoholic cirrhosis. Chronic alcoholics without liver disease fell within the normal range (3/28—11%). Patients with cryptogenic cirrhosis, PBC, and CAH, did not differ from the control population. Liver biopsies examined by orcein stain and electron-microscopy showed no evidence of intrahepatic viral particles.

These findings are suggestive of an association between previous hepatitis B infection and the development of chronic alcoholic liver disease. This association requires confirmation and further investigation.

Orcein positive copper associated protein in childhood liver disease

J. EVANS, P. J. SCHEUER, B. ARCHER, S. P. NEWMAN, AND S. SHERLOCK (Departments of Medicine, Histopathology, and Medical Physics, Royal Free Hospital, London) An orcein positive copper associated protein (CAP) has been shown in adult hepatocytes and is believed to be an abnormal copper protein1. CAP has not been described in children.

Liver sections from six neonates (including two foetuses) without liver disease and four groups of age-matched children, n = 38 (normal subjects, non-cirrhotic liver disease, cirrhosis, intrahepatic cholestasis of childhood (IHCC)) were semi-quantitatively assessed for CAP and copper by staining with orcein and rhodanine respectively. Liver copper concentration was measured by neutron activation analysis.

In eight normal children with normal liver copper concentration, CAP was absent. Liver copper levels were increased in six of six neonates (physiological rise) and 12 of 14 cases of IHCC. Orcein positive material was found in liver cells of all six neonates, in the 12 patients with IHCC and raised hepatic copper concentrations, and one cirrhotic patient with normal hepatic copper concentration.

When hepatic copper concentration exceeded 3.9 μmol/l in neonates and IHCC, rhodanine and orcein stains were usually moderately positive. The results lend further support to a relationship between CAP and copper and the positive results in normal neonates support the view that CAP is a physiological substance and not a consequence of biliary obstruction.

Reference


Serum CEA—another test of liver function?

K. R. HINE, S. N. BOOTH, AND P. W. DYKES (Department of Immunology, University of Birmingham) Serum carcinoembryonic antigen (CEA) is of little value in the early diagnosis of alimentary cancer. However, none of the extensive clinical
reports has tried to assess its value in a prospective series of undiagnosed patients. Three-hundred-and-eighty-one patients in four diagnostic categories have been investigated by standard techniques and by estimation of CEA. In patients with upper gastrointestinal symptoms, lower gastrointestinal symptoms, and iron deficiency anaemia, CEA was of limited prospective value in the diagnosis of malignancy. However, in the group of 74 patients with abnormal liver function tests and hepatomegaly, 38 had a final diagnosis of malignant disease and in nearly all cases (90%) the CEA level was raised, compared with 53% of those with benign conditions. All values in patients without neoplasia were below 45 ng/ml, whereas, in 43% of those with malignancy, this value exceeded. This information, in a number of instances, was not obtainable in any other way. CEA was markedly superior to other laboratory tests (alkaline phosphatase, ESR, 5-nucleotidase) in discriminating between the two groups.

It would appear that CEA might be of more use in evaluating this type of clinical problem that many of the indices currently employed.

**Use of alpha-1-antitrypsin (a1-AT) as an endogenous marker to detect protein-losing enteropathy**

C. L’HIRONDEL, C. FLORENT, C. DESMAZURES, C. AYMES, AND J. J. BERNIER (Hôpital Saint-Lazare, Paris) a1-antitrypsin is not destroyed by pancreatic enzymes and is found in the faeces; it was therefore used to measure the plasma protein loss into the gastrointestinal tract.

We examined 28 patients without gastrointestinal disease and 19 with protein-losing enteropathy diagnosed either by isotopic technique or by evidence of active chronic inflammatory bowel disease.

Stools were collected during a four to 10 day period. Blood samples were taken at the beginning and the end of the study. a1-AT was measured through an immunodiffusion technique using commercially available plates.

The following measures were made daily: a1-AT faecal concentration, a1-AT faecal loss (F), a1-AT faecal clearance (C).

\[ C = \frac{F}{P} \]

where \( P \) is the mean a1-AT serum concentration.

Our results show that a1-AT faecal concentration and a1-AT faecal loss were higher in patients than in control subjects (\( p < 0.01 \)); (2) the determination of a1-AT clearance was more sensitive to separate the two groups (\( p < 0.001 \)); (3) the mean clearance calculated over a three day period allowed a diagnosis of protein-losing enteropathy in all patients except one; (4) no false positive results were observed in control subjects.

This simple and reliable test will provide new facilities in patients’ diagnosis and in management of the treatment.

**Is faecal alpha-1 antitrypsin measurement a reliable diagnostic test of protein-losing enteropathy?**

M. R. HAENENY, J. FIELDS, R. A. CARTER, R. A. THOMPSON, AND P. ASQUITH (Regional Immunology Laboratory, Department of Nuclear Medicine and Metabolic Research Unit, East Birmingham Hospital, Birmingham) It has been suggested that estimation of a1-antitrypsin (a1AT) in random faecal samples provides a reliable index of intestinal protein loss.

We have measured faecal a1AT concentrations in 20 adults (11 men, nine women), average age 39 years (range 18-60 years), investigated for suspected protein-losing enteropathy in a metabolic unit where accurate faecal collections were possible. The diagnoses were Crohn’s disease (six), ulcerative colitis (three), contaminated bowel syndrome (three), coeliac disease (two), chronic active hepatitis (two), sigmoid diverticulosis (one), small intestinal ischaemia (one), chronic pancreatitis (one), and intestinal lymphangiectasia (one). Alpha-1-antitrypsin concentrations in stool homogenates were measured by single radial immunodiffusion using a monospecific rabbit anti-human a1AT and the results expressed in three ways: mg a1AT/g dry weight of stool/day, mg a1AT excreted/day, or as a ratio of faecal/serum a1AT. Mean (five day) faecal a1AT results were compared with the simultaneous faecal loss of 51Cr-albumin and with serum levels of albumin, immunoglobulins and orosomucoid, and with faecal nitrogen excretion.

No significant correlation was found between faecal a1AT results and 51Cr-albumin loss or other parameters, thus seriously questioning the validity of faecal a1AT estimation as a screening test for protein-losing enteropathy.

**Radio-opaque markers for faecal fat**

F. G. SIMPSON, G. P. HALL, J. KELLEHER, AND M. S. LOSOWSKY (University of Leeds Department of Medicine, St. James’s Hospital, Leeds) Inert markers enable accurate faecal fat estimations with only short collection periods but chemical estimation of marker is needed. Radio-opaque beads have been tried as inert markers in normal subjects. Estimation is simple by radiography. We report their use in routine faecal fat studies in patients, and comparison with established markers, polyethylene glycol 4000 (PEG) and chromium sesquisoxide (Cr2O3).

Thirty-seven patients with a variety of diagnoses were maintained on constant diet and given PEG 500 mg tds, Cr2O3 500 mg tds, and beads 8 tds. After five days’ equilibration, faeces were collected into polyethylene bags for two day periods. A total of 84 collections was made. Water was added before homogenising with an external mechanical paddle. The homogenised specimens were frozen, radiographed, thawed, and an aliquot removed for analysis.

Over a wide range of faecal fat (2-62.0 g/day), recovery of markers, as expected, varied widely (28-282%, mean 94%, for PEG; 33-244%, mean 97%, for pellets; 28-250%, mean 99-7% for Cr2O3). There were very close correlations between excretions of all markers (correlation coefficients between 0.92 and 0.95).

Corrected faecal fats also correlated extremely closely (correlation coefficients between 0.92-0.97).

Thus radio-opaque pellets are reliable and offer advantages over traditional markers for routine faecal fat balances. Estimation is precise and simple. Faeces can be collected, homogenised, and the marker determined in the polyethylene bag used for collection.

**References**


Use of \(\text{\textsuperscript{99m}Tc}\)-HIDA in hepatobiliary scintigraphy

T. V. TAYLOR, D. C. CARTER, G. P. MCLoughlin, A. MILLER, and M. D. SUMERLING (Departments of Clinical Surgery, Medical Physics, and Radiology, Edinburgh Royal Infirmary) Scintigraphic imaging of the hepatobiliary system has been recently improved by the availability of \(\text{\textsuperscript{99m}Tc}\)-pyridoxyldiglutamate. \(\text{\textsuperscript{99m}Tc}\) HIDA may have advantages over pyridoxyldiglutamate, but has not been fully evaluated in man.

Thirty patients with a variety of hepatobiliary pathology were investigated. After an overnight fast, 2 mCi of \(\text{\textsuperscript{99m}Tc}\) was given intravenously and the patient scanned continuously for one hour. When functioning normally the liver was visualised within five minutes, excretion into the common bile duct, gall bladder, and duodenum occurred at an early stage and the Tc\(^{1/2}\) of the tracer in the blood stream was 20 minutes. In complete obstructive jaundice, isotope was excreted through the renal tract without visualisation of the liver.

The technique was combined with oral cholecystography and ultrasonography in 20 patients presenting as emergencies with abdominal pain and suspected biliary disease. Agreement between \(\text{\textsuperscript{99m}Tc}\)-HIDA and cholecystography in terms of gall bladder filling occurred in 18 patients but in addition stones were visualised on three cholecystograms. Ultrasonography also agreed with HIDA scintigraphy in 18 patients with abnormal gall bladders. Scintigraphy was particularly useful in assessing the jaundiced patient. We have not witnessed any adverse side-effects from the use of this radiopharmaceutical.

References


Ultrasonography in the differential diagnosis of jaundice

C. RUBIO, L. BERGER, J. DOOLEY, and S. SHERLOCK (Departments of Medicine and Diagnostic Radiology, Royal Free Hospital, London) This investigation assessed the accuracy of ultrasound in the differential diagnosis of jaundice. One-hundred-and-sixteen jaundiced patients referred to the Royal Free Hospital for ultrasonography were studied from 1 September 1977 to 30 April 1978. The diagnosis of 'surgical' or 'medical' jaundice was based on the presence or absence of dilated ducts. Fifty-one were found to have dilated, and 65 non-dilated ducts. Forty-nine of the 51 (96%) had obstructed ducts confirmed by percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), surgery, or necropsy. In 39 of these 49 (79-5%) the site of obstruction was correctly identified. However, the cause was diagnosed in only 14 (28-5%).

All 65 patients with non-dilated ducts had a definite diagnosis established by liver biopsy, PTC, ERCP, surgery, or necropsy. In six of the 65 (9-2%) the ultrasound findings were incorrect. Four of these six had moderately dilated ducts and stones in the common bile duct, one had sclerosing cholangitis, and the other had clots in the common bile duct visualised by PTC.

Ultrasound differentiated between 'medical' and 'surgical' jaundice in 93% of the patients. As a non-invasive technique, it should be used routinely in the investigation of the jaundiced patients.

Non-invasive techniques in the diagnosis of jaundice—ultrasound and computer

A. THEODOSII, P. J. WHEELER, R. PICKFORD, J. LAWS, and R. WILLIAMS (Liver Unit, King's College Hospital and Medical School, Denmark Hill, London) This study aimed to document the accuracy in differentiating between medical and surgical types of jaundice using ultrasound in 84 patients and computer-aided diagnosis (CAD) in 169. Fifty of these patients were evaluated by both techniques.

The correct final diagnosis was established in all patients by prolonged clinical follow-up and by histology in those without extrahepatic biliary obstruction, and by laparotomy or necropsy in those with.

Two of 84 patients were technical failures for ultrasound. Seventy-five of the remaining 82 (91-5%) were correctly separated into medical and surgical categories. One-hundred-and-fifty-two of the 169 patients (90%) were similarly correctly classified with CAD.

In the 50 patients evaluated by both techniques correct diagnostic separation was achieved in 43 (86%) by ultrasound and in 42 (84%) by computer. This group of patients included the two ultrasound technical failures, both being correctly identified as surgical by the computer. Six of the computer diagnoses were false negatives and therefore missed a surgical diagnosis and two were false positive. All the errors for ultrasound represented false negatives.

These data therefore indicate that ultrasound and CAD are similarly effective in distinguishing between medical and surgical causes of jaundice.

Clinical value of the dumping provocation test: an independent assessment

O. LAWAETZ, Y. ARTAS, D. N. L. RALPHS, and M. HOBBSLEY (Department of Surgical Studies, The Middlesex Hospital, London) The dumping provocation test (150 ml 50% glucose orally) may be used to evaluate patients with symptoms after gastric surgery. Patients with a fall in plasma volume, derived from haematocrit measurements, of at least 9% have been found to experience dumping symptoms during the test. Using this objective criterion alone 81 patients were tested (on average four years) after a variety of operations for duodenal ulceration; a fall in plasma volume of less than 9% being deemed a negative test and a 9% or greater fall a positive one. Before the test an independent observer had placed the patients into a dumping (39) or non-dumping (42) group after assessment of their clinical symptoms.

A positive test showed an 83% correlation with the group assessed as 'dumpers' symptomatically. The predictive value of a negative test was 85%. Twelve patients, who experienced pain after ordinary meals and subsequently were shown to have recurrent ulceration, had negative tests.

The clinical value of the test lies particularly in its ability to sort patients with any postprandial symptoms after gastric surgery. We conclude, that a positive dumping provocation test confirms the diagnosis of dumping with nearly 100% accuracy. A negative test indicates the need for further investigations.

References


2Meurling, S. (1953). Post cibal symptoms after
partial gastrectomy for peptic ulcer, Acta Societatis Medicorum Upsaliensis, Supp. 3.

Clinical relevance of gastrin assay

T. P. CORBISHLEY, R. C. G. RUSSELL, AND S. J. MITCHELL (Departments of Surgical Studies and Nuclear Medicine, The Middlesex Hospital, London) The estimation of the level of plasma gastrin is of established value in the diagnosis of the Zollinger Ellison syndrome (ZES). The clinical impact of gastrin radioimmunoassay has been assessed by a review of five years experience. In 1972 gastrin levels were estimated in three patients; subsequent years have shown a progressive rise (1973: 50; 1974: 273; 1975: 275; 1976: 775; 1977: 992) The proportion of patients with raised gastrin levels (50 pmol/l) has increased (1974: 14%; 1977: 34%), but the percentage whose raised gastrin level was confirmed as being due to the ZES has remained at approximately 4% (n = 64).

A survey of all patients from whom samples were received in 1977 was conducted to determine the reasons for the request. The indications for requesting the gastrin level in 423 replies were: gastrinostestinal haemorrhage 25% (75% sample levels 50 pmol/l); perforation 10% (70% 50 pmol/l); aggressive peptic ulcers 35% (66% 50 pmol/l); multiple peptic ulcers 17%; jejunal ulcer 6%; diarrhea 21%; failed surgery 28%. Of those patients whose diagnosis of ZES was confirmed the commonest presenting symptom was aggressive peptic ulceration (37%). The clinician considered that the gastrin estimation was of clinical relevance in 80% patients and 35% replies considered that the gastrin result had influenced clinical management.

This survey suggests that the radioimmunoassay of gastrin is of value in clinical gastroenterology and that presentation alone will not accurately denote the ZES.

Fats leave the stomach faster when ingested as homogenised meals than when eaten as solids.1 We measured fat absorption after ingestion of identical meals in different physical forms, to achieve different rates of gastric emptying. Meals consisted of hamburger, bread, butter, ice cream, and water (total fat 15%). Four subjects received homogenised meals, nine ate the solid meal; meals contained 1H-glycerol triester (1H-GTE) and/or sucrose octoate (14C-SPO) as non-absorbable lipid-phase markers.2 Intubation allowed gastric sampling and total recovery of contents proximal to a jejunal balloon, 30 cm beyond the duodenojejunal junction.

1. Ratios of lipid markers to total fatty acids (TFA) in the stomach remained constant. Homogenised meals emptied in four hours; % of marker emptied/h was 53, 27, 11, 9. Solid meals required six hours to empty; (%/h) 6, 17, 18, 21, 23, 15. Total amounts of fat emptied were not different: homogenised 8.7 ± 1.4 g, solid 7.7 ± 0.7 g.

2. Ratios of lipid marker/TFA in jejunal samples were higher after the solid meal, reflecting greater absorption of fat after this meal.

3. Total fat absorbed was greater after solid meals (81.1 ± 3.4%) than after homogenised meals (47.5 ± 10.7%; p < 0.005). In conclusion, fat ingested with a solid meal emptied from the stomach much more slowly but was absorbed from the proximal intestine more efficiently.

References


Sodium dependence of glucose and maltose absorption in the jejunum in man

G. I. SANDLE, R. W. LOBLEY, AND R. HOLMES (University Department of Gastroenterology, The Royal Infirmary, Manchester) In vivo work suggests Na+-dependent disaccharide-linked glucose transport from maltose in addition to the monosaccharide transport system.1 To investigate this, 20 cm segments of proximal jejunum were perfused (flow rate 18 ml/min) by double-lumen tube in four normal subjects using solutions in sequence containing 56 mM glucose + 122 mM Na+ (I), 56 mM glucose without Na+ (II), 28 mM maltose + 122 mM Na+ (III), and 28 mM maltose without Na+ (IV). Solutions were made isotonic with mannitol as appropriate and contained PEG 5 g/l. Glucose absorption
(mmol/10 min ± SEM) from II (3·80 ± 0·4) was 23·5% less (0·005 < p < 0·01) than from I (4·97 ± 0·19). Similarly, absorption from IV (4·91 ± 0·52) was 22·5% less (0·025 < p < 0·05) than from III (6·29 ± 0·37).

Glucose absorption from III (6·29 ± 0·37) was significantly higher than from I (4·97 ± 0·19; 0·005 < 2r < 0·01) while net water absorption (ml/10 min ± SEM) from III (25·49 ± 3·45) was significantly lower than from I (36·58 ± 3·38; 0·025 < 2r < 0·05). Similarly, glucose absorption from IV (4·91 ± 0·52) was significantly higher than from II (3·8 ± 0·4; 0·02 < 2r < 0·025), while net water secretion was no different (0·30 ± 17·49 and 45·31 ± 8·07, respectively).

Maltose hydrolysis rates (mmol/10 min ± SEM) with IV (4·21 ± 0·13) and IV (4·19 ± 0·24) were not significantly different (0·45 < p < 0·475).

It is concluded that (1) Na⁺-independent disaccharidase-linked glucose transport was not confirmed in man, (2) glucose was absorbed more rapidly from 28 mM maltose than 56 mM glucose during both net absorption and secretion of water, (3) maltose hydrolysis was unaffected by low intraluminal sodium concentrations.

Four normal subjects were perfused with isotonic solutions containing PEG 5 g/l, 21 mM NaCl and appropriate amounts of mannitol: 35 mM maltose; 222 mM glucose; 35 mM maltose + 222 mM glucose; 111 mM maltose. Absorption rates of glucose were 6·23 ± 0·99, 10·16 ± 0·34, 11·58 ± 0·34, and 11·33 ± 0·53 respectively. Net water and sodium movements (secretion in all) were 42·08 ± 5·84, 24·62 ± 3·76, 32·42 ± 10·63, 42·89 ± 6·18 and 6·97 ± 0·38, 5·86 ± 0·58, 6·17 ± 0·80, 6·18 ± 0·77 respectively.

Five normal subjects were perfused with isotonic solutions containing PEG 5 g/l, 21 mM NaCl and mannitol: 111 mM glucose; 111 mM maltose; and 111 mM glucose + 111 mM maltose. Absorption rates of glucose were 6·39 ± 0·43, 8·51 ± 1·11, and 10·98 ± 1·5 respectively. Net water and sodium movements (secretion in all) were 30·25 ± 3·34, 51·16 ± 6·07, 35·04 ± 3·16 and 8·34 ± 1·10, 8·24 ± 1·52, 7·47 ± 1·13 respectively.

Thus (1) increasing secretion of water and sodium may accompany increasing glucose absorption, (2) water and sodium move together, the direction depending on sodium concentration perfused rather than rate of glucose absorption, (3) secretion of water is greater with maltose than with equimolar glucose.

Glucose-stimulated intestinal fluid secretion: an acquired intestinal transport defect

J. DAWSON, H. J. F. HODGSON, T. J. PETERS, AND V. S. CHADWICK (Department of Medicine, Royal Postgraduate Medical School, London) Diarrhoea in common variable immunodeficiency is often associated with jejunal mucosal abnormalities, bacterial overgrowth, or giardiasis.¹ We studied a patient with profound secretory diarrhoea in whom extensive investigations failed to show any of these abnormalities.

To elucidate the pathophysiology of the diarrhoea we perfused the jejunum, ileum, and colon with various isosmotic solutions by triple lumen perfusion techniques.² In the jejunum, fluid and electrolyte transport were normal using saline and bicarbonate-saline solutions. However, addition of 30 mM glucose to the perfusate stimulated profound net secretion of water (125 ml/30 cm segment/h), sodium (16·4 mmol/h), and chloride (26·6 Mmol/h). In contrast, glucose stimulated absorption in normal subjects.

Glucose itself was absorbed normally. An exactly similar phenomenon was demonstrated in the ileum. Perfusion of the whole colon with saline demonstrated net secretion of water and electrolytes.

Failure of glucose-stimulated absorption was not due to failure of glucose absorption per se nor was there any brush border abnormality demonstrable by electron microscopy or analytical subcellular fractionation.³ A hormonal mechanism for this glucose stimulated secretion is unlikely since it was not abolished when the perfusion was repeated during intravenous somatostatin infusion. The phenomenon represents a hitherto undescribed acquired intestinal transport defect.

References

Movement of water and sodium during the absorption of glucose and maltose in the jejunum in man

G. J. SANDLE, R. W. LOBLEY, AND R. HOLMES (University Department of Gastroenterology, The Royal Infirmary, Oxford Road, Manchester) Twenty centimetre segments of proximal jejunum were perfused in three normal subjects (flow rate 21 ml/min) with isotonic glucose-saline solutions containing PEG 5 g/l:

(1) 55·5 mM glucose, 122 mM NaCl;
(2) 166·5 mM glucose, 66 mM NaCl;
(3) 222 mM glucose, 39 mM NaCl;
(4) 277·5 mM glucose, 11 mM NaCl. Glucose absorption (mmol/10 min ± SEM) increased from 5·34 ± 0·61 with (1) to 9·73 ± 0·77 with (4), while net water movement (ml/10 min ± SEM) changed from 35·3 ± 5·27 absorbed (1) to 15·89 ± 4·91 secreted (4). Net sodium movement (mmol/10 min ± SEM) changed from 3·79 ± 0·67 absorbed (1) to 5·5 ± 0·11 secreted (4).

Drug and dietary modification of carbohydrate absorption

R. H. TAYLOR, D. J. A. JENKINS, AND R. NINEHAM (introduced by J. J. MISIEWICZ) (Department of Gastroenterology, Central Middlesex Hospital, London; Department of Regius Professor of Medicine, Radcliffe Infirmary, Oxford, and University Physiology Laboratory, Oxford) Small intestinal lesions are known to alter the pattern of carbohydrate absorption. The development of a glycosidase-inhibitor (BAY 5421) makes possible controlled carbohydrate malabsorption without affecting transit. These studies aim to show that gastrointestinal absorption of carbohydrate can be modified to flatten the post-prandial glycaemia curve without producing nonabsorption. Sucrose with and without BAY g 5421 was given to healthy male volunteers. Serial measurements were made of blood glucose and breath hydrogen.

BAY g 5421 200 mg given with 50 g sucrose produced a reduction in the control blood sugar rise of 76 ± 7% (p < 0·001, n = 6). Calibration of the subjects for hydrogen production from unabsorbed carbohydrate with lactulose
25 g indicated that 63 ± 15% (p < 0.002, n = 6) of the original sucrose was not absorbed. Fifty milligrams of the drug with 50 g sucrose produced no significant hydrogen or flattening of the curve.

However, when half the test meal carbohydrate was given as starch, 50 mg of BAY g 5421 reduced the 30 minute mean peak blood sugar rise by 22% (p < 0.01, n = 4) and by a further 42%—that is, total 64% (p < 0.05, n = 4)—when fibre (guar gum) was added, with no breath hydrogen evidence of carbohydrate malabsorption.

We conclude that modification of glucose absorption may allow flattening of the post-prandial glycaemia curve without producing malabsorption and its symptoms. These results may explain the absence of post-prandial glycaemia without symptoms of carbohydrate malabsorption in gastrointestinal enzyme deficiency states.

Ursodeoxycholic acid reduces fatty diarrhoea after ileal resection

T. M. COX, G. VAN BERGHE HENEGOUVEN, AND V. S. CHADWICK (Department of Medicine, Royal Postgraduate School, London, and Universitystieinklijke Voor Invendige Zieken, Nijmegen) Profuse steatorrhoea is a major problem after ileal resection. It results largely from decreased micellar solubilisation of fat due to intraluminal bile salt deficiency. Attempts to correct the fat malabsorption by feeding sodium taurocholate reduced steatorrhoea but aggravated diarrhoea, because of bacterial conversion to deoxycholate in the colon.

Activity studies showed that ursodeoxycholic acid (UDCA), unlike deoxycholic acid and chenodeoxycholic acid, did not produce colonic secretion. Accordingly, a trial of bile acid replacement with UDCA was undertaken in six patients with ileal resections and steatorrhoea. After a four day control period 0.25 g UDCA was given before meals for four days; during this period analysis of bile showed that UDCA accounted for 51% of bile acids. At this low dose, daily faecal fat fell by a mean of 15% (p < 0.05) with 11% decrease in faecal weight (p < 0.01). In addition, UDCA rich-bile was shown in vivo to be an effective mixed micelle-former with dietary fat. When 4g UDCA was given daily in a further patient, there was a 40% reduction in faecal weight and a 50% reduction in faecal fat.

These studies show that bile acid replacement with UDCA reduces steatorrhoea and diarrhoea after ileal resection.

References


Composition and enzymes of crypt and villus cells in the small intestine of folate deficient rats

JACQUI BADCOCK AND A. M. TOMKINS (Department of Human Nutrition, London School of Hygiene and Tropical Medicine, London) Mucosal folate deficiency of the small intestine is a feature of infective malabsorption syndromes, but its contribution to diarrhoea is uncertain. Experimental folate deficiency is associated with the development of diarrhoea, morphological lesions, and a reduction in total mucosal DNA, RNA, and protein, to 44%, 59%, 63% of control animals, respectively. Fractions of epithelial cells from villi and crypts of control animals, showed higher ratios of RNA/DNA and protein/DNA in villus than crypt cells (259 ± 13 vs. 165 ± 6 and 3.77 ± 0.23 vs. 2.06 ± 0.18, p < 0.01). In folate deficiency RNA/DNA and protein/DNA were greater, especially at the villus tips, compared with controls (395 ± 34 and 5.35 ± 0.32, p < 0.01). Radioautography showed a delay in cell migration time in folate deficiency (4-7 vs. 10-2 μM/h in controls, p < 0.001) and might suggest that the compositional changes of the epithelial cells represent 'hypermaturity'. In villus tip fractions, succrase activity per cell was sufficiently increased for total gut sucrase not to be decreased by folate deficiency. However, Na-K-ATPase activity per villus tip cell did not increase in folate deficiency and total mucosal Na-K-ATPase was lower. This suggests that, despite the longer migration time permitting acquisition of enzymes for carbohydrate absorption, the cells did not acquire increases of enzymes associated with sodium and water transport, and this may contribute to the diarrhoea of mucosal folate deficiency.

References


The British Society of Gastroenterology

Absorption of dietary cholesterol and hepatic cholesterol synthesis in cirrhosis

M. PONZ DE LEON, F. ZIRONI, P. LORIA, A. SMERIERI, AND N. CARULLI (Istituto di Clinica Medica, Policlinico, Modena, Italy) Dietary cholesterol absorption and synthesis, mainly in the liver, are among the factors that regulate blood cholesterol levels. The low cholesterol levels frequently observed in cirrhosis,1,2 therefore, could either be due to an impaired cholesterol absorption or to a reduced synthesis. We aimed to assess how these two variables could contribute to the genesis of hypocholesterolaemia in cirrhosis.

We evaluated hepatic cholesterol synthesis by determining the activity of the hydroxymethylglutaryl-CoA reductase (HMG-CoA-R), the rate limiting enzyme in cholesterol synthesis, in surgical liver biopsies of six patients undergoing portacaval shunt. Cholesterol absorption was estimated in 12 cirrhotic patients by feeding a standard dose of C-14 labelled cholesterol, plus sitosterol-H-3 as a non-absorbable marker, and by measuring the recovered radioactivity in the faecal neutral sterol fraction for the next six days. All patients had marked hypcholesterolaemia (102 ± 14 mg/dl SDM).

Results showed that HMG-CoA-R activity was 59.7 ± 6.6 pmol/m/mg prot. in a control group of eight patients operated on for duodenal ulcer and 30.2 ± 5.6 (p < 0.01, 50.5% decrement) in the cirrhotics. Cholesterol absorption was 38.4 ± 4% of the administered dose in normal controls and 27.9 ± 10% (p < 0.05, 27.4% decrement) in the cirrhotics.

We conclude that both a decreased cholesterol synthesis and a low cholesterol absorption could explain the low cholesterol levels observed in cirrhosis; synthesis, however, seems to be more affected than absorption.

References


Dynamics of gall-bladder contraction in response to different cholecystokinin

JANE M. OLIVER, J. F. REY, AND R. F. HARVEY (Department of Medicine, Bristol Royal Infirmary and Frenchay Hospital,
Bristol) Gall-bladder contraction begins very soon after food is eaten and tonic contraction continues for at least one to two hours after a normal meal. These effects are mediated mainly by the peptide hormone cholecystokinin-pancreozymin (CCK).

Radioimmunoassay studies indicate that several different molecular forms of CCK are present in the body. The molecular sizes of the three known forms, cholecystokinin(33 aminoacids, CCK-33) CCK-variant (39 aminoacids, CCK-39), and octapeptide (eight aminoacids, CCK-8) are very different.

The dynamics of action of different CCK preparations on rabbit gall-bladder muscle strips were studied in vitro using a superfusion technique. Gall-bladder contraction begins within a few seconds after contact with each CCK preparation. Peak contraction was reached after a mean of 8-16 minutes (range 6-8 to 9-0 minutes). Initial speed of contraction was greater with CCK-8 than CCK-33 (50% of peak contraction in 1.75 ± 0.35 vs. 2.55 ± 0.64 min, p < 0.05). Gall-bladder relaxation was significantly slower after cessation of CCK-33 superfusion than after CCK-8 (Tₐ = 5.39 ± 0.75 vs. 4.67 ± 0.63 min, p < 0.05). The Boots CCK preparation (Boots Company Ltd., Nottingham) produced both faster contraction (50% contraction in 2.03 ± 0.29 vs. 2.65 ± 0.62 min, p < 0.05) and faster relaxation after ending the superfusion (Tₐ = 3.53 ± 0.37 vs. 5.39 ± 0.75, p < 0.001) than GIH cholecystokinin (Karolinska Institute, Stockholm).

We conclude that (1) different molecular forms of CCK have qualitatively different effects on the gall-bladder, and (2) the effects of the Boots preparation of CCK are consistent with the finding that it contains mainly smaller molecular forms of the hormone.

Investigation of hormonal control of gall bladder storage in man: studies using indocyanine green (ICG)

O. G. BJÖRNSSON, J. DAWSON, G. R. GREENBERG, R. F. MCCLOY, T. PANAYIOTIDIS, T. E. ADRIAN, S. R. BLOOM, AND V. S. CHADWICK (Department of Medicine, Royal Postgraduate Medical School, London) Cholecystokinin (CCK) is known to promote gall bladder contraction. Recent investigations suggest that pancreatic polypeptide (PP) may have opposite actions leading to gall bladder storage. To investigate this hypothesis we have measured gall bladder storage using intravenously administered ICG as a marker of biliary output by a duodenal perfusion technique, in healthy controls, and after cholecystectomy. In the steady state a gall bladder storage fraction was calculated from any decrease in duodenal ICG output.

In normal fasting subjects the gall bladder storage fraction was 0.8-1.0. Fasting storage patterns were abolished by simulating the interprandial state with intravenous secretin (0.1 CU/kg/h) and caerulein (10 ng/kg/h). As predicted, the storage fraction in fasting cholecystectomy patients was zero. During secretin-caerulein infusion in normal subjects, bovine PP at physiological plasma concentrations significantly (p < 0.001) decreased ICG output. In contrast, BPP did not change ICG output in cholecystectomised patients.

We conclude that low circulating levels of secretin and caerulein abolished fasting gall bladder storage patterns. Under these conditions PP promoted gall bladder storage.

Failure of PP to decrease ICG output in cholecystectomised patients suggests a direct action on the gall bladder.

Real-time ultrasound—a new method for investigating gall-bladder dynamics

M. H. ORNSTEIN, A. PALFRAMAN, AND H. MEIRE (Northwick Park Hospital Harrow) (introduced by I. M. BAIRD) Little is known of gall-bladder dynamics. Research methods have been indirect or invasive, depending on the metabolism of oral radiographic agents or the risks of intravenous agents. Radiation dosage is appreciable and magnification is a major problem, compounded by movement of the gall bladder during contraction. Radio-isotopic scanning suffers from similar disadvantages and intubation is non-physiological.

These problems can be overcome by the use of real-time, grey-scale, ultrasound B-scanning, and in this preliminary study we have investigated gall-bladder emptying in 13 normal male fasting volunteers. The gall bladder is visualised using a hand held probe which is rotated until the largest possible area of gall bladder is obtained on the video-screen and this is measured on a photographic copy using planimetry. After an initial scan a standard fatty meal is taken and scans repeated at frequent regular intervals for 30-45 minutes.

In keeping with previous work, despite considerable initial variation the gall bladders showed a remarkably similar, almost linear, reduction in size reaching 76 ± 2.5% (mean ± SEM) at 15 minutes, 50 ± 2.6% at 30 minutes, but only 41.3 ± 4.3% at 40 minutes—that is, with this stimulus complete emptying does not occur.

We conclude that this is a straightforward non-invasive and physiological method of studying dynamic gall-bladder function, superior to previous methods.

References


Direct measurement of the first pass extraction of bile acids by the liver in man

I. T. GILMORE AND R. P. H. THOMPSON (Gastrointestinal Laboratory, Rayne Institute, St. Thomas' Hospital, London) The hepatic extraction of bile acids is assumed to be almost complete but direct measurements have not been previously reported in man. We report such measurements for cholic and glycocholic acid in control subjects and patients with chronic liver disease (CLD) and compare them with indirect estimates of extraction ratio (ER) from the ratio of the oral and intravenous clearances.

After intravenous injection or constant infusion of 14C-glycocholic acid blood samples were taken simultaneously from peripheral and hepatic veins. The ER in three control subjects was 90 ± 2%, 84 ± 3%, and 88 ± 1% (mean ± SD). Extraction was greater than for simultaneously measured indocyanine green. In five patients with CLD, ER was reduced to 24-65%. The ER of 14C-cholic acid in two controls was 72 and 70% and in eight patients with CLD was from 17-74%; indirect measurement of oral and intravenous clearances overestimated ER by a mean of 64% of the directly measured value.

Thus a high hepatic extraction of bile acids in man is confirmed by direct measurement and is greater for conjugated than unconjugated cholic acid. This is impaired in CLD where indirect estimates from oral and intravenous clearance may overestimate liver function.
Effect of chenodeoxycholic acid (CDCA) on cholesterol absorption in man

M. PONZ DE LEON, P. LORIA, R. IORI, AND N. CARULLI (Istituto di Clinica Medica, Policlinico, Modena, Italy) The effects of CDCA administration in reducing biliary cholesterol secretion and desaturating bile have been related to the inhibition of CDCA on hepatic cholesterologenesis. However, only part of the biliary cholesterol is neosynthesised in the liver and cholesterol from other sources, including dietary cholesterol, can be secreted in bile. Accordingly, biliary saturation may be reduced by inhibiting cholesterol absorption. We decided, therefore, to investigate the effect of CDCA feeding on cholesterol absorption.

Eight volunteers were given a standard meal containing 500 mg cholesterol, 5 μCi cholesterol-C-14, and 10 μCi sitosterol-H-3 to correct losses from sources other than absorption. The radioactivity of the faecal neutral sterol fraction was determined for the next six days to provide an estimate of unabsorbed cholesterol. The same subjects were restudied after a 20 day treatment with CDCA (15 mg/kg/day). Changes in biliary lipid and bile acid composition were also taken into account.

During treatment, the proportion of CDCA in bile increased from 35-0 ± 12-4% (SD) to 75-5 ± 5-7% of total bile acids and percent saturation of bile fell from 6-4 ± 2-1 to 4-9 ± 1-0%. Cholesterol absorption was 33-7 ± 14% of the given dose in basal condition and decreased to 15-5 ± 9-8% (p < 0-01) after treatment.

We conclude that, given in doses effective to desaturate bile, CDCA seems to decrease dietary cholesterol absorption. This effect could contribute to the desaturation of bile during CDCA treatment.

References

Rowachol, a proprietary essential oil preparation, lowers hepatic microsomal HMGCoA reductase and dissolves cholesterol gallstones

G. D. BELL, J. DORAN, ALIYA MIDDLETON, B. MIDDLETON, C. R. RICHMOND, AND D. A. WHITE (Department of Therapeutics, City Hospital, Nottingham, Department of Surgery, General Hospital, Nottingham, and Department of Biochemistry, Medical School, Queen's Medical Centre, Nottingham) Rowachol, a proprietary preparation of essential oil, is freely available in the UK. Like chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA), R lowers the lithogenic index of human bile. We have studied, in the rat, the effect of R on HMGCoA reductase—the rate limiting enzyme for cholesterol biosynthesis. R significantly (p < 0-01) inhibited hepatic HMGCoA reductase. This is of interest, as R has also been reported to lower serum cholesterol level in man.

Twenty-seven patients with radiolucent gallstones were treated with R (two capsules tds) for periods of six months or more. There was evidence of gallstone dissolution and/or disappearance in seven of the 27 patients. The drug was well tolerated and no evidence of hepatotoxicity or other serious side-effects have emerged.

We conclude that prolonged oral administration of R appears to be safe. This compound and possibly other terpene substances merit more detailed consideration as cholelitholytic agents either alone or in combination with CDCA or UDCA.

References

Plenary

Gut hormone profile after gut resection

H. S. BESTERMAN, S. R. BLOOM, T. E. ADRIAN, N. D. CHRISTOFIDES, D. L. SARSON, C. N. MALLINSON, A. PERO, AND R. MODIGLIANI (Royal Postgraduate Medical School, London, Lewisham Hospital, London, Ospedale Mauritiano, Turin, Italy, and Hopital St Lazare, Paris, France) We have previously demonstrated a greatly exaggerated postprandial rise in plasma enteroglucagon in coeliac disease and have postulated that it might be exerting a compensatory trophic effect on the intestinal mucosa. We therefore went on to study the effect of intestinal resection on enteroglucagon and other gut hormones, where similar mechanisms might be operating. Gut hormone release was investigated after ingestion of a standard test breakfast (530 Kcal) in 18 patients with partial ileal resection, in nine patients with partial colonic resection, and in 11 normal subjects. Gut resection had been undertaken for inflammatory bowel disease, neoplasia, radiation, fibrosis or trauma, a minimum of one year before study. Basal and peak levels of
pancreatic polypeptide, gastrin, motilin, and enteroglucagon were all significantly raised in the group with ileal resection. In marked contrast, however, only pancreatic polypeptide levels were significantly increased in patients with colonic resection.

Thus we find striking abnormalities in the levels of enteroglucagon and a number of other gut hormones in patients with partial ileal resection, which may reflect compensatory mechanisms. The gut hormone profile in ileal resection differs markedly from that seen in colonic resection and also from that in coeliac disease, in ulcerative colitis and in Crohn's disease.

Reference

Improved diagnostic accuracy of a modified oral pancreatic function test (PFT)

C. J. MITCHELL, C. S. HUMPHREY, A. W. BULLEN, J. KELLEHER, AND M. S. LOSOWSKY (University Departments of Medicine and Surgery, St. James's Hospital, Leeds) The oral PFT depends upon urinary recovery of p-aminobenzoic acid (PABA) released by chymotrypsin hydrolysis of orally given N-Benzoyl-L-Tyrosyl-p-aminobenzoic acid (Bz-Ty-PABA). However, falsely abnormal results are frequently found in bowel or liver disease, as PABA recovery is also affected by abnormal absorption or hepatic conjugation. Furthermore, pancreatic dysfunction may coexist with liver or bowel disease.

To improve diagnostic accuracy, we have compared urinary recovery from Bz-Ty-PABA with that from an oral dose of pure PABA, giving a PABA excretion index:

\[
\text{PEI} = \frac{\% 8 \text{h urine PABA recovery from oral Bz-Ty-PABA}}{\% 8 \text{h urine PABA recovery from oral pure PABA}}
\]

We have assessed the modified test in six normal subjects, seven patients with chronic pancreatic insufficiency, and 11 patients with small bowel disease (six) or chronic liver disease (five) in whom the conventional oral PFT was falsely abnormal.

The mean PEI for normal subjects was 1:1 (range 0:82-1:18) but was markedly reduced in the pancreatic patients at 0:51 (range 0:29-0:67). The PEI was similar to normal for patients with bowel disease (mean 0-9, range 0-72-1-30) and liver disease (mean 0-99, range 0-73-1-9).

Thus the PEI distinguished abnormal results due to pancreatic disease from falsely abnormal results in liver and bowel disease. We conclude that the modified oral PFT greatly improves diagnostic accuracy.

Breath hydrogen in pneumatosis cystoides intestinalis

J. GILLON, K. TADESSE, R. F. A. OGAN, S. HOLT, AND W. SIRCUS (Gastrointestinal Unit and Wolfson Laboratory, Western General Hospital, Edinburgh, Gastrointestinal and Liver Service, Royal Infirmary, Edinburgh) Pneumatosis cystoides intestinalis (PCI) is a rare condition of unknown aetiology. Previous research suggested that bacterial gas-production may be an important factor, and the hydrogen content of the cysts lends support to this view, since \( H_2 \) is not produced by human cells.

We have studied breath \( H_2 \) excretion in six patients known to have PCI. Subjects 1 and 2 had greatly raised fasting breath \( H_2 \) levels (normal 0-20 ppm) and both showed a considerable rise after 50 g glucose orally. Both had gross PCI at the time of the test. Subject 6 had a high-normal basal breath \( H_2 \) and a moderate rise in response to 50 g glucose. She had undergone resection of localised sigmoid PCI two months earlier. Three subjects showed a negative response, only one of whom had PCI demonstrable on plain x-ray.

The high basal breath \( H_2 \) in subjects 1 and 2 implies constant bacterial \( H_2 \) production, and the response to glucose in subjects 1, 2, and 6 suggests small intestinal colonisation. Subject 2 achieved clinical and radiological remission after three weeks' oral tetracycline, basal breath \( H_2 \) returning to normal.

These results lend support to the hypothesis that gas production by bacteria may be an important aetiological factor in PCI.

Reference

Duodenal iron uptake in vitro: studies in iron overloaded subjects

T. M. COX AND T. J. PETERS (introduced by

DR V. S. CHADWICK) (Department of Medicine, Royal Postgraduate Medical School, London) A method for determining initial rates of iron uptake into human duodenal biopsies has been developed. Uptake of iron in normal subjects was saturable over the concentration range 18-450 \( \mu \text{mol/l} \) and was shown to have the features of active transport.

Because there is evidence that idiopathic haemochromatosis is caused by inappropriate intestinal absorption of dietary iron, the kinetics of uptake were studied in duodenal biopsies taken from patients with both primary and secondary iron overload. Five patients with idiopathic haemochromatosis (two untreated; three partially treated—mean time from venesection 34 ± 6 months) and five patients with iron overload secondary to thalassaemia major (two), alcoholic cirrhosis (two), and hereditary spherocytosis (one), were studied.

Compared with 11-15 controls, uptake at 18, 90, and 180 \( \mu \text{mol/l} \) medium iron concentrations was increased up to 85% in haemochromatosis \( (p < 0.005, p < 0.025, p < 0.05, \) respectively), indicating an increased tissue affinity for iron. In contrast, no significant abnormality in the kinetic behaviour of iron uptake by biopsies from patients with secondary iron overload was found.

These data indicate that there is a specific abnormality of the mucosal iron carrier in idiopathic haemochromatosis, which is not a consequence of iron overload.

Reference

Transnasal bile duct catheterisation after endoscopic sphincterotomy: a method for biliary drainage, perfusion, and sequential cholangiography

P. B. COTTON, P. G. J. BURNEY, AND R. R. MASON (Gastrointestinal Unit, The Middlesex Hospital, London) Most ductal stones pass spontaneously after adequate sphincterotomy, but repeat endoscopic cholangiography is necessary to prove this. We have evolved a method which reduces the need for repeat endoscopy, and has other advantages. Immediately after sphincterotomy a fine Teflon tube is passed deep into the biliary system and preferably looped in the common hepatic duct. The endoscope is remov-
Will ursodeoxycholic acid (UDCA) replace chenodeoxycholic acid (CDCA) as the medical treatment of choice for gallstone dissolution?

G. WILLIAMS, P. N. MATON, G. M. MURPHY, and R. H. DOWLING (Gastroenterology Unit, Guy’s Hospital and Medical School, London) Both CDCA and UDCA desaturate bile and dissolve cholesterol-rich gallstones but, despite more difficult synthesis and greater cost, UDCA still may have advantages over CDCA. To study this, in 120 patients with radiolucent gallstones in functioning gall bladders treated with CDCA and 22 similar patients given UDCA, we compared dose, efficacy, symptoms, and side-effects.

Biliary cholesterol saturation indices correlated with bile acid dose (mg kg⁻¹ day⁻¹) for CDCA (r = 0.43; p < 0.01) and UDCA (r = 0.855; p < 0.001). Minimum doses required to desaturate bile were 4.0 mg kg⁻¹ (CDCA) and 2.5 mg kg⁻¹ (UDCA) and to desaturate bile consistently—14.5 mg CDCA (excluding obese and resistant patients) and 9.5 mg UDCA. Mean doses required to dissolve gallstones were 14.2 mg CDCA and 8-0 mg UDCA.

After six months' treatment with mixed UDCA doses (5-15 mg kg⁻¹ day⁻¹) seven of the eight patients (88% showed partial or complete gallstone dissolution compared with 27 of 35 (77%) given <13 mg CDCA kg⁻¹ day⁻¹.

Dose-related diarrhoea occurred in 36 of 84 (43%) treated with CDCA but in only one of 22 (4%) given UDCA.

Dose-related hypertransaminasaemia was seen in 33% of CDCA-treated patients but never occurred with UDCA.

We conclude that UDCA has comparable efficacy to CDCA, is effective in two-thirds of the dose, and does not cause diarrhoea. If long-term absence of diarrhoea, hypertransaminasaemia, and toxicity are confirmed, UDCA seems likely to replace CDCA.

References

Serum methionine: a biochemical measure of the severity of liver failure

A. J. KNEILL, D. J. COLLINS, and R. ROBINSON (Warwick Hospital, Warwick) Lack of a simple test of the severity of liver failure (like the blood urea in kidney failure) hinders the selection of patients for artificial liver support. Coma is the indication for treatment, although allowing the disease to progress so far reduces the chances of success. We have developed a simple automated assay of serum methionine to assist in patient evaluation.

Our reference range is 20-60 μmol/l. We have used the test routinely for over a year.

Serum methionine concentrations increase rapidly as liver failure develops. Values above 300 μmol/l are associated with encephalopathy. The onset and disappearance of encephalopathy correlated with the rise and fall of serum methionine during acute liver failure in two patients who recovered. Values are low (<20 μmol/l) during the first 24 hours after paracetamol poisoning, then increase as liver damage progresses. No increases occur in simple hepatitis or obstructive jaundice. Serum methionine is moderately increased (100-200 μmol/l) in severe kidney failure. We attribute this to product inhibition of methionine metabolism by creatinine.

Measurement of serum methionine adds precision to assessing patients in liver failure, and permits early identification of cases who may need artificial liver support.

References

The British Society of Gastroenterology

The case for high dose antacid therapy in duodenal ulcer

R. A. KEENAN, R. H. HUNT, DIANA VINCENT, B. WRIGHT, and G. J. MILTON-THOMPSON (Royal Naval Hospital, Haslar, Gosport, Hampshire) High dose antacid therapy accelerates the healing of duodenal ulcer.

Using a technique previously described we have studied such a regimen over 24 hours in 11 patients with duodenal ulcers in remission. Patients received 30 ml magnesium and aluminium hydroxide liquid (Wyeth) with 140 mmol buffering capacity to pH 3-0, or placebo, one and three hours after main meals and on retiring. Gastric juice was sampled hourly throughout the study, measured for pH and returned to the stomach.

Antacid caused a highly significant reduction in intragastric acidity between meals but the effect was less after mid-night. Mean 24 hour intragastric hydrogen ion activity was 57-8 ± SEM 2-9 mmol on placebo and antacid reduced this by 50% to 29-1 ± 2-6 mmol (p < 0.001). From midnight to 0700 activity was reduced by 31% from 81-9 ± 4-5 mmol (placebo) to 56-5 ± 4-8 mmol (antacid) (p < 0.001).

Cimetidine 1 g a day was studied in a separate group of 15 duodenal ulcer patients. Mean 24 hour intragastric hydrogen ion activity was reduced by 50% from placebo and nocturnal activity by 66%.

High dose antacid therapy appears as effective as histamine H₂-receptor antagonists in reducing intragastric acid over 24 hours but has less effect on night secretion.

References

Trial of plasmapheresis in patients with Crohn’s disease

G. HOLDSTOCK, A. FISHER, C. LOEHRY, and T. HAMBLIN (Royal Victoria Hospital, Bournemouth) Immune complexes have been found in patients with chronic inflammatory bowel disease, particularly during relapse. It has been suggested that these complexes may be an important factor in the pathogenesis of the disease, especially the extragastrointestinal com-
The British Society of Gastroenterology

Plasmapheresis has been shown to be effective at removing immune complexes, with clinical improvement in patients with SLE—a disease known to be associated with high levels of circulating immune complexes.

With these facts in mind, we have performed a pilot study of plasmapheresis in patients with Crohn's disease. One newly diagnosed patient and five with long-standing disease were studied. Patients were selected because of their unacceptable steroid requirements.

Patients were studied for up to six months. The mean steroid requirements for the five long-standing cases was reduced from 17.5 to 2.5 mg prednisolone daily. Thirteen clinical relapses were controlled by plasmapheresis alone and all patients remained well. All had high levels of circulating immune complexes, and these levels were reduced after plasmapheresis. Levels of these complexes correlated with the severity of patients' symptoms.

Plasmapheresis is worthy of future investigation as a steroid-sparing agent in Crohn's disease and may give further clues to the pathogenesis of the disease.

---

CLINICAL MEDICAL/CLINICAL SURGICAL

Aetiological aspects of finger clubbing (FC) in inflammatory bowel disease (IBD)

G. KITIS, H. THOMPSON, AND R. N. ALLAN (Nutritional and Intestinal Unit, and Department of Pathology, The General Hospital, Birmingham) The aetiology of FC, commonly associated with IBD, is unknown. Suggested aetiological factors include the extent of disease activity, the degree of fibrosis in tumours, and reflex mechanisms of which the vagus nerve may be the afferent pathway.

We assessed FC by objective measurement of nail profile and hyponychial angles. The mean profile angle was 166° ± 5° (±4.5) and the mean hyponychial angle 178° (±5.0) in 118 healthy volunteers, 51 of whom had duplicate measurements made.

Finger clubbing (defined as one or both angles > 165 SD from the control mean) was present in 40% of patients with Crohn's disease (75/189 patients), 15% with ulcerative colitis (15/101), and 8% with proctitis (2/25).

Finger clubbing was significantly associated with disease activity assessed by laboratory indices (p < 0.001), the degree of fibrosis in resected specimens (p < 0.001), and macroscopic disease in areas of the gut innervated by the vagus nerve (p < 0.001). FC was significantly associated with the severity assessed by the need for surgical intervention (p < 0.001) and corticosteroid therapy (p < 0.01). There was no correlation between FC and duration of disease.

These data have identified that disease activity, severity of disease, and degree of fibrosis and vagal innervation are important in the pathogenesis of FC associated with IBD.

References

Functional bowel disorder: a new perspective

W. GRANT THOMPSON AND K. W. HEATON (University Department of Medicine, Bristol Royal Infirmary, Bristol) Although 30-50% of patients referred to gastroenterologists suffer from functional disorders, their prevalence in the community is unknown.

A questionnaire about functional gastrointestinal symptoms was administered to 301 apparently healthy British subjects in young, middle-aged, and elderly categories. Abdominal pain, a feeling of incomplete evacuation after defaecation, urgency, scybala, runny stools, straining at stool, borborygmi, distention, heartburn, and laxative use were very common.

The spastic colon syndrome occurred in 13-6% and was identifiable by cluster analysis. These subjects had abdominal pain relieved by defaecation and significantly associated with mucus, feeling of incomplete evacuation, urgency, distension, and more frequent, looser stools following pain onset. Dyspepsia consisting of pain, usually in the upper abdomen, not relieved by defaecation, and associated with heartburn, occurred in 7%. A further 3-7% had painless diarrhoea characterised by frequent runny stools and a strong association with urgency. Six per cent suffered painless constipation defined as frequent straining at stool and significantly associated with scybala, less frequent bowel movements, mucus, feeling of incomplete evacuation, distension, and increased laxative use.

Thus, four distinct functional bowel syndromes existed in at least 30% of subjects who were not patients. Studies of functional gastrointestinal disorder must take into account the large number of uncomplaining sufferers in the community.

Therapeutic trial of Ativan, Buscopan, and Fybogel in the irritable bowel syndrome

J. A. RITCHIE AND S. C. TRUELOVE (Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford) A double-blind controlled therapeutic trial of factorial design has been used to test the therapeutic effects of lorazepam (Ativan), hyoscine N-butyl bromide (Buscopan), and ispaghula husk (Fybogel) in 12 randomised blocks of eight patients with the irritable bowel syndrome. Therapeutic success implied a definite symptomatic improvement within one month, maintained over the following two months. Failure implied either a lack of improvement or relapse within the three-month duration of the trial.

Each of the three agents conferred some benefit but the only one to give results that were significantly better than placebo was Fybogel. There was no evidence of interaction between them. When the eight possible combinations of treatment were analysed, no successes occurred among the 12 patients who received only dummy preparations of the three agents. Seven successes occurred among the 12 who received potent preparations of all three. Groups receiving one or two of the potent preparations obtained intermediate scores.

These results show that the effects of drugs used in treating the irritable bowel syndrome can be additive. Other combinations deserve to be similarly studied if the efficacy of medical treatment is to be improved.

Colonic bacterial activity, bile cholesterol saturation, and the pathogenesis of gallstones

T. S. LOW-BEER AND SHEILA NUTTER (Selly Oak Hospital, Birmingham) This study investigates how colonic metabolism of bile acids affects biliary bile acid composition and cholesterol saturation.
Eleven healthy men ingested metronidazole 2 g daily for 10 days to inhibit anaerobic bacteria. Fasting gall-bladder bile was aspirated from the duodenum before, at the end of 10 days, and one month after stopping metronidazole. The relative concentrations of cholate, chenodeoxycholate, and deoxycholate were measured, and also those of phospholipid and cholesterol. Bile cholestero saturation was then calculated, and the two-tailed paired $t$ test applied.

Metronidazole decreased deoxycholate from a mean of 24% to 7% returning to 22% a month later. Chenodeoxycholate changed from 33% to 46% and back to 33% ($p < 0.001$ throughout), cholate from 44% to 48% to 45% ($p < 0.005$ and not significant respectively). Bile cholestero saturation fell in 10 of the 11 subjects, from a mean of 1·00 to 0·83 and then increased in all to a mean of 1·11 after discontinuing metronidazole ($p < 0·01$ and $< 0·001$ respectively).

This study demonstrates that deoxycholate absorption selectively reduces Chenodeoxycholate concentrations in bile, previously shown to result from suppression of chenodeoxycholate synthesis in the liver. With decreasing deoxycholate absorption bile cholestero saturation falls, with increasing absorption cholestero saturation rises, also shown previously. Diets known to decrease the absorption and recirculation of deoxycholate (such as high-fibre diets) should reduce the risk of gallstones.

Observations on the treatment of primary pneumatosis coli

S. HOLT AND R. C. HEADING (University Department of Therapeutics and Clinical Pharmacology, The Royal Infirmary, Edinburgh) Successful treatment of pneumatosis coli by high flow oxygen therapy has been reported but there is no agreement on the optimum procedure. We have treated five patients with primary pneumatosis coli, using high flow oxygen therapy in a standardised manner with symptomatic and radiological resolution of disease. In each case, the extent of disease and its response to therapy were defined endoscopically and radiographically. Bacteriological examination of the patients’ stool and colonic mucosa revealed no qualitative or quantitative abnormalities and the flora was not altered to any great extent by oxygen therapy. Clinical and radiological remission has been maintained in all patients with follow-up periods ranging from six months to three years. Intermittent high flow oxygen therapy provides a safe and comfortable form of treatment for patients with symptomatic pneumatosis coli. Its success is apparently not dependent on eradication of anaerobic bacteria from faeces or colonic mucosa.

Adenocarcinoma in Barrett’s oesophagus: a report of 16 cases

J. DEES, M. VAN BLANKENSTEIN, AND M. FRENKEL (introduced by J. R. Bennett) (Erasmus University Rotterdam, Department of Internal Medicine II, Rotterdam) Barrett’s oesophagus (BO) may be a pre-malignant lesion. Only about 40 cases of adenocarcinoma in BO have been published. Since 1974 we have diagnosed 16 cases at endoscopy. Endoscopic criteria were (1) histologically confirmed normal gastric mucosa above the tumour; (2) no tumour in the cardia region of the stomach.

In a group of 5300 patients undergoing upper gastrointestinal endoscopy between 1974 and 1978, 71 cases of primary oesophageal carcinoma were seen, 44 (62%) squamous cell- and 27 (38%) adenocarcinomas. The relatively low percentage of squamous cell carcinoma is the result of patient selection. The 27 adenocarcinomas form an unselected group, 16 of these (59%) were found in BO. The 71 cases of primary oesophageal carcinoma are part of a group of 161 patients referred to a regional cancer centre. Therefore, in this unselected group, at least 16 (10%) of the oesophageal carcinomas were found in BO. This percentage should be contrasted with a 0·6% prevalence of BO in the 5300 upper gastrointestinal endoscopies. These findings support the hypothesis that BO entails an increased risk of oesophageal carcinoma.

Review of the results of dilatation in the management of benign oesophageal strictures in a surgical clinic

F. H. YOUAN AND C. W. VENABLES (Newcastle University Hospitals, Newcastle upon Tyne) The management of benign peptic oesophageal strictures remains controversial. Since 1972 we have adopted an initial conservative approach to this problem using endoscopic dilatation. This paper presents a review of our material and the results of management.

Between 1972-77, 47 patients (32 male) have had endoscopically confirmed benign oesophageal strictures under our care. A total of 133 dilatations have been performed using the following techniques: (1) forcible dilatation with endoscope (38), (2) Eder Peustow (42), (3) blind bougie (53), with only two perforations (1·3%). One dilatation alone was successful in relieving symptoms in 23 patients but 15 needed three or more dilatations. Sixteen patients have had surgical management after dilatation either for coexistent duodenal ulceration, hiatus hernia, or failure of conservative management.

In conclusion, this study demonstrated that dilatation is a safe method of management. The Eder Peustow dilator appears to be the best if the endoscope alone is unsuccessful. With this conservative approach surgical intervention can be avoided in many patients.

Perforation of duodenal ulcers in the elderly

M. R. THOMPSON (Royal Devon and Exeter Hospitals (Wonford and Heavitree), Exeter) In a six-year review of duodenal perforation in Exeter it was found that 40% (36 out of 89) of duodenal perforations occurred in patients over the age of 70 years and approximately 50% of these were women. Perforation time (PT) was longer in the over 70s (over 70, $PT = 25·1 h \pm 4·3\%$; $N = 26$; $o f 70, PT = 12·7 h \pm 1·7\%$; $N = 47$ $p < 0·005$). The mortality rate in patients over the age of 70 years was 35% compared with 4% for the under 70s. The major factors in the cause of death in the over 70s was PT and chronicity of the ulcer. In patients over 70 years with a PT of > 18 h there was a 54% mortality rate compared with 8% in patients with a PT of < 18 h. Seven of the nine elderly patients who died developed severe complications of a persisting chronic ulcer—namely, bleeding, pyloric stenosis, and perforation—before dying three to 43 days after admission.

It is suggested that, although simple suture is adequate in elderly patients who have perforation for less than 18 hours, paradoxically those that have perforated for more than 18 hours and who have a chronic ulcer require more extensive surgical procedures.

These data show that there is room for
improvement in the management of this condition and that better results can be achieved only by earlier diagnosis and a change in the surgical management.

Intraoperative tests for completeness of vagotomy

M. H. THOMPSON, R. C. N. WILLIAMSON, P. W. DAVIES, W. K. ELTRINGHAM, AND D. JOHNSTON (Department of Surgery, Bristol Royal Infirmary, Bristol) The results of peptic ulcer surgery would be improved if all vagotomies were complete, but this is likely to be achieved only by using an intraoperative test. Two tests have been evaluated: the Grassi test using pentagastrin stimulation and an intraluminal pH electrode, and the Burge test, using direct nerve stimulation and intragastric pressure measurement.

In phase 1, 25 patients had highly selective vagotomy for duodenal ulcer. After completion of vagotomy both tests were performed and no further dissection was done. One week post-operatively gastric secretion was measured. Hollander's criteria, peak acid output (insulin) and peak acid output (pentagastrin) were used to measure completeness of vagotomy. The Burge test gave misleading results. (All Hollander positive patients were in the Burge 'negative' group). Patients with negative Grassi test had significantly lower postoperative secretion than those with positive Grassi test (p = 0.048).

In phase 2, if the Grassi test was positive, more vagal nerve fibres were cut, and postoperative secretion measured as in phase 1. All patients were Hollander negative, and measured postoperative secretion was not significantly greater than in the Grassi negative patients in phase 1.

We conclude that the Grassi test is helpful in producing complete vagotomy, but that the Burge test is not.

Evaluation of a non-invasive insulin test

T. V. TAYLOR, H. SHARMA, B. R. PULLAN, AND H. B. TORRANCE (Department of Clinical Surgery, University of Edinburgh, and Manchester Royal Infirmary) A direct relationship between acid output and intragastric accumulation of $^{99m}Tc$ has led to the development of a non-invasive method of assessing gastric function. The possibility of performing an insulin test non-invasively has been investigated in 39 patients. After an overnight fast $^{99m}Tc$ (1 mCi) was given intravenously and 40 minutes later insulin 0-2 u/kg IV. Five minute $\gamma$-camera computer frames were taken for 120 minutes. Under basal conditions a slow and steady accumulation of intragastric activity occurs, but if a secretory response to insulin is obtained a sharp rise in activity above the predicted course of the curve is seen, as the stomach is the only organ in the field of study capable of concentrating the isotope.

A quantitative sharp rise in the intra-gastric activity was obtained in the first hour after insulin in 18 of 21 patients with an intact stomach. Of 18 patients who had undergone recent vagotomy and who were insulin negative by routine testing, 17 failed to show a sharp rise in intra-gastric activity after insulin. Of the 18 insulin positive results some gastric emptying was seen on the scan in 15, whereas of the 17 insulin negative patients only four had observed gastric emptying of $^{99m}Tc$.

References


CLINICAL SURGICAL/HORMONES

Preliminary results of a modified Hill-Larrain procedure for gastroesophageal reflux

E. A. MORMUS, M. OESTER, P. FUCHS-JENSON, AND A. CSENDES (introduced by Rory McCloy) (Surgical-gastroenterological Dpt., Kommunehospitalet, Aarhus University, Denmark) Thirty-six patients suffering from failure of at least two years medical treatment were operated on for gastroesophageal reflux (heartburn + regurgitation). Four had additional duodenal ulcer, three were previously operated on for duodenal ulcer, and two for reflux oesophagitis. All had a positive acid reflux test, eight also had radiological reflux. All had histological and 12 also macroscopic signs of oesophagitis. Four of the patients had fibrotic stenosis with dysphagia. The operative steps were: (1) partial cell vagotomy; (2) cardioplasty with one non-absorbable suture; (3) calibration with a 12 mm bougie; (4) gastropty to the median arcuate ligament.

One patient died postoperatively from oesophageal tear. One had a postoperative subphrenic abscess drained. The other operations were uncomplicated.

Observation at two to 20 months: initial dysphagia subsided in one to two months. All were relieved from symptoms of gastroesophageal reflux. In one a positive acid reflux test could be induced and in another radiological reflux was still observed. In the rest examinations were negative.

Adding of partial cell vagotomy reduces gastric acid secretion, provides better technical access, and secures against unintended vagotomy.

Importance of an intact, innervated pyloric antrum in the control of gastric emptying of liquids in man

C. M. WHITE, VALERIE Poxon, M. R. B. KEIGHLEY, AND J. ALEXANDER-WILLIAMS (The General Hospital, Birmingham) Studies in dogs suggest that gastric emptying of liquids is controlled by the tone of the body and fundus of the stomach; the antrum and pylorus appear unimportant. In man the gastric outlet does seem important. The faster emptying and the diarrhoea and dumping after vagotomy and pyloroplasty may be caused by the pyloroplasty or the denervation of the antrum as well as the body and fundus.

We have examined the separate effects of pyloroplasty and vagal denervation. Thirty-three patients with uncomplicated duodenal ulcer were randomly allocated to one of four operations: proximal gastric vagotomy (PGV) N = 10; proximal gastric vagotomy and pyloroplasty (PGV + P) N = 8; total gastric vagotomy (TGV) N = 7; total gastric vagotomy and pyloroplasty (TGV + P) N = 8. The emptying of 10% dextrose was studied before and after operation.

Early passive emptying was significantly faster than preoperatively after all operations (PGV p < 0.01; PGV + P p < 0.025; TGV p < 0.01; TGV + P p < 0.025—paired t test). Later emptying was unchanged after PGV but was significantly faster after all the other operations (PGV + P p < 0.025; TGV...
p < 0.001; TGV + P p < 0.005—paired t test).

Our results indicate that, although proximal gastric denervation causes faster early emptying, the innervated intact terminal antrum and pylorus are important during the later emptying of liquids.

References


Why do patients die after surgical treatment for peptic ulcer haemorrhage even when diagnosis is established?

C. W. VENABLES (Newcastle University Hospitals (NGH and RV), Newcastle upon Tyne) The value of emergency endoscopy in the management of upper GI bleeding is being questioned because of a failure to demonstrate changes in mortality. Clearly endoscopy cannot affect the outcome unless it modifies management. Since 1972 emergency endoscopy has been attempted in all cases of upper GI bleeding coming to surgery in the two hospitals in which I work. This paper presents an analysis of 111 cases treated surgically between 1972-78 with an analysis of various factors that might be related to mortality.

In Hospital A, 73 patients were operated upon with an overall mortality of 8.2%, while in hospital B, the mortality was 25%. Various factors have been analysed, including age; sex; diagnosis; delays before admission, endoscopy, and operation; surgical expertise, length, and technique; blood transfused; other diseases present. The analysis demonstrates that the most important factors are delays in admission and the presence of coexistent diseases.

It is concluded that comparisons between mortality figures should be made only if all other factors are comparable.

Failure

W. P. SMALL (Gastric Follow-Up Clinic, Western General Hospital, Edinburgh) A strangely neglected index of failure of surgery for peptic ulcer is that the patient keeps coming back.1 On whom does this clinical load fall? What is the cost? Can failure be avoided?

The records of 25 'good' results and 25 'bad' results2 randomly selected from the Gastric Follow-Up Clinic have been compared in an attempt to answer these questions.

The consequences of surgical failure weigh most heavily on the laboratories, the radiologists and the endoscopists. Reoperation is not so large a burden.

Specialised units attract failures and with them disproportionate demands on investigative techniques. The need to recognise this work load in terms of facilities and staffing is obvious.

The investigation of failure costs at least £500, to which must be added the costs of inpatient management, work loss, and social security.

Failure is potentially avoidable. It stems from misjudged operation in patients with no clear indications for surgery and from the complications of radical surgery. To invest in the avoidance of failure by better investigation, better selection, lesser operations, and, indeed, fewer operations makes sense.

The trend towards proximal vagotomy and the use of cimetidine as an alternative to surgery is to be encouraged.

References


Is it necessary to add neomycin to metronidazole for oral prophylaxis in colonic operations?

S. VALLANCE, B. JONES, M. R. B. KEIGHLEY, J. ALEXANDER-WILLIAMS, AND Y. ARABI (The General Hospital, Birmingham) Prophylactic neomycin (N) and metronidazole (M) will reduce postoperative sepsis but it has been suggested that prophylactic M alone may abolish aerobic and anaerobic sepsis. However, oral M has no influence on colonic microflora.

The aim of this study has been to compare the influence of M alone with that of M and N on the incidence of sepsis after elective colonic resections. So far 52 patients have entered a double blind placebo controlled study: 26 patients received M alone (200 mg tds) and an equal number received M (200 mg tds) and N (1 g tds) for two days preoperatively. The groups were similar with respect to age, sex, and method of bowel preparation.

Wound sepsis occurred in 50% of patients receiving M alone compared with only 23% after M and N. The incidence of perineal sepsis, septicemia, and anastomotic dehiscence was similar in the two groups. The overall incidence of septic complications was 57-6% after M alone and only 38-4% after M and N.

The preliminary results of this study indicate that neomycin should be added to metronidazole for effective antimicrobial prophylaxis in bowel surgery.

References


Variation in antral gastrin concentration and the effect of gastritis

R. J. McFARLAND, J. S. SLOAN, AND K. D. BUCHANAN (The Queen's University of Belfast, Northern Ireland) Antral gastrin concentration has been studied by endoscopic biopsy in 34 patients with non-ulcer dyspepsia, 19 with acute gastritis, 19 with duodenal ulcer, and six with pernicious anaemia. Three adjacent antral biopsies were taken from each patient and buffer extract assayed for gastrin. Mucosal gastrin concentration was markedly higher in pernicious anaemia (159 ± 65 ng/g, M ± SE), compared with non-ulcer dyspepsia, (35 ± 6 ng/g), acute gastritis (43 ± 14 ng/g), and duodenal ulcer (18 ± 4 ng/g). A striking feature was the marked variation within biopsies from the same patient confirming previous reports of uneven gastric mucosal concentration. To determine the effect of local mucosal pathology on gastrin cell population, a separate study on 35 gastrectomy specimens was carried out using immunofluorescent and immunoperoxidase techniques. The numbers of detectable immunoreactive gastrin cells diminished with increasing severity of gastritis and

The British Society of Gastroenterology
very few were detected in the presence of intestinal metaplasia.

Thus it appears that the presence and severity of antral gastritis is one important factor in the marked variation in gastrin cell numbers and mucosal concentration seen in small biopsies and should be taken into account in their assessment.

Simple technique for the demonstration of polypeptide-secreting endocrine cells in human small intestinal biopsies

C. Shaw, J. S. Sloan, and P. Titterington (introduced by K. D. Buchanan) (Departments of Medicine and Pathology, Queen's University of Belfast) Present methods for the demonstration of polypeptide-secreting endocrine cells occurring in the mucosa of human small intestine require elaborate and tedious fixation techniques which are not applicable to the routine laboratory.

We have developed a simple technique using a liquid phase fixative which has resulted in the easy identification of polypeptide-secreting endocrine cells in human small intestinal mucosa obtained at biopsy. These include cells containing gastrin inhibitory polypeptide, vasoactive intestinal polypeptide, gastrin, somatostatin, secretin, and glucagon immunoreactive materials. Demonstration may be achieved using either immunofluorescent or immunoperoxidase techniques. The tissue morphology is well preserved, thus permitting routine histological assessment—a factor of considerable importance when small intestinal biopsies are under analysis for clinical purposes.

The fixative procedure will allow the assessment of the role of small intestinal endocrine cells in a variety of disorders, and has been successfully used to demonstrate polypeptide-secreting endocrine cells in other tissues including antrum, pancreas and large bowel.

Gastrointestinal hormone patterns associated with interdigestive and postprandial motor activity in the human proximal bowel

W. D. W. Rees, J.-R. Malagelada, and V. L. W. Go (introduced by S. F. Phillips) (Gastroenterology Unit, Mayo Clinic, Rochester, Minnesota, USA) We have characterised interdigestive and postprandial motor patterns in the human proximal bowel1. In the present study, relationships among these motor patterns and blood levels of gastrointestinal hormones were examined. Intraluminal pressure was recorded from the antrum, duodenum and jejunum of six healthy subjects using intraluminal transducers. On the first day, fasting motility and blood levels of gastrin, motilin, glucagon, and gastric inhibitory polypeptide were measured at 15 minute intervals for eight hours. On the second and third days, four different liquid meals (carbohydrate; protein; lipid; combined) were randomly administered (two each day) during phase II interdigestive activity and levels of gastrin and motilin were measured.

Fasting gastrin, glucagon, and gastric inhibitory polypeptide remained low and constant, while motilin showed cyclic variation (range: 138 ± 21 to 523 ± 96 pg/ml). Motilin peaks were associated with antroduodenal phase III activity in two subjects, but such a relationship was absent in the remaining subjects. Protein and combined meals produced significant gastrin release (3200 ± 500 and 1400 ± 400 pg/60 min) and lipid caused significant motilin release (1100 ± 400 pg/60 min). All meals inhibited interdigestive activity, the duration being significantly longer for lipid and combined meals1. Conclusions were that (1) fluctuation in fasting motilin correlates poorly with interdigestive motility while other hormones show little variation; (2) feeding disrupts motor cycles, protein and combined meals releasing gastrin and lipid releasing motilin.

Reference

Bombesin evokes calcium-dependent amylase secretion in the isolated mouse pancreas

O. H. Petersen (Department of Physiology, University of Dundee Medical School) The tetradecapeptide bombesin evokes pancreatic secretion by a direct action on the plasma membrane of the acinar cells1. The calcium dependence of this process and the possible interactions with other secretogogues have been investigated using a sensitive on-line fluorometric method for determining amylase output2 from isolated superfused segments of mouse pancreas.

Bombesin (10^-8 M) (maximally stimulating concentration3) caused a marked, but only transient increase in amylase output during exposure of the tissue to calcium-free solution containing EDTA (calcium chelator). Admission of calcium (50 μM to 2-6 mM) during sustained maximal stimulation caused an immediate dose (calcium) dependent increase in amylase secretion. In the presence of calcium the secretory response to bombesin was sustained. Removal of calcium during sustained bombesin stimulation caused an immediate abolition of the stimulant-evoked secretion. In the case of submaximal acetylcholine or caerulein stimulation, bombesin had no effect. In the case of submaximal acetylcholine or caerulein stimulation, bombesin caused an increase in secretion up to the maximal level.

Bombesin evokes enzyme secretion through exactly the same calcium dependent mechanism4 as acetylcholine and cholecystokinin.

References

Measurement of trypsin concentration in duodenal juice using a radioimmunoassay

G. Lake-Bakaar, S. Mckavanagh, C. E. Rubio, and J. A. Summerville (introduced by Professor Dame Sheila Sherlock) (Department of Medicine, Royal Free Hospital, London) Trypsin output in duodenal aspirate following pancreatic stimulation with either a Lundh meal or cholecystokinin-pancreozymin (CCK-PZ) and secretin remains a standard test of pancreatic function. However the usual method of trypsin estimation, based on enzymatic hydrolysis of the substrate p-tosyl-L-arginine methyl ester-HCl (TAME) has several disadvantages, including autodegradation of the enzyme which precludes storage before estimation.

A radioimmunoassay (RIA) has been described for the estimation of trypsin even in the presence of inhibitors such as Trasylol. The trypsin concentration in duodenal aspirate has been determined by RIA in a total of 25 estimations and compared with the enzymatic method. The effect of Trasylol on the stability of trypsin in duodenal aspirate stored at −70°C was also studied.

Enzymatic activity correlated well with the mass of trypsin obtained by RIA (r < 0.005, Student’s t test). No cross-reactivity
was shown with Trasylol. Storage of duodenal aspirate led to rapid loss of trypsin (mean 9-9% range 6-3-19%) at four weeks. This was completely prevented by the addition of Trasylol (p < 0-05, Student’s paired t test).

We conclude that RIA determination of duodenal juice trypsin concentration is a useful alternative method to enzymatic analysis and should be performed whenever prior storage of the enzyme is necessary, since autodigestion can be completely prevented with Trasylol.

**Effect of age on hepatic drug metabolism and on the response to enzyme induction**

N. CARULLI, M. PONZ DE LEON, G. ROMANO, AND R. IORI (Istituto di Clinica Medica, Policlinico, Modena, Italy) Although age-dependence of drug metabolism is a widely held concept, only few reports focus attention on the impairment of hepatic drug metabolism in human aging. In this study we evaluated the metabolism of three model drugs in the attempt to define the role of the various determinants of hepatic drug metabolism, such as drug metabolising capacity, liver blood flow, and plasma protein binding of the drug.

Two groups of subjects were studied: (1) 21 elderly subjects (mean age 79 ± 7-9 years) and (2) 21 young adults (mean age 27-2 ± 6-9 years). Liver function and other appropriate tests ruled out hepatic, renal, or metabolic dysfunctions. The subjects had not been medicated for at least four weeks before testing. In subgroups of seven subjects for each age group, aminopyrine, tolbutamide and propranolol pharmacokinetics were evaluated. Tolbutamide and propranolol metabolism was studied in the same subjects also after phenobarbital treatment (100 mg/day for seven days).

In the elderly group the metabolic clearance of aminopyrine (67-5 ± 12 ml/min) and tolbutamide (9-3 ± 1-6 ml/min) was significantly lower (p < 0-01) than in the young group (106-7 ± 15-2 and 18-9 ± 3-2 respectively). Propranolol clearance did not differ in the two groups (1-08 ± 0-3 l/min versus 1-12 ± 0-41). In the elderly subjects phenobarbital treatment produced an increase of tolbutamide clearance (+70% of the basal value) greater than in young subjects (+21%). The treatment did not change the propranolol clearance.

We conclude that decreased hepatic drug metabolism in elderly subjects seems to be due mainly to a reduced activity of the hepatic drug metabolising system.

**Alcohol reduces liver acetaldehyde dehydrogenase**

W. J. JENKINS AND T. J. PETERS (introduced by V. S. CHADWICK) (Department of Medicine, Hammersmith Hospital, London) Acetaldehyde, the first product of ethanol metabolism, is more toxic than alcohol itself. Alcoholics display higher blood levels of acetaldehyde than non-alcoholics given the same dose of ethanol; but the cause of this difference is unknown. Normally acetaldehyde is rapidly removed by oxidation to acetaldehyde, which catalyses acetaldehyde dehydrogenase, which has been little studied in man, and there has been no previous work on its activity or intracellular localisation in fresh human liver.

We have developed an assay for acetaldehyde dehydrogenase, and determined its specific activity in liver biopsies from controls and non-cirrhotic alcoholics. The specific activity in alcoholics (43-4 ± 6-6 mU/mg protein) was significantly less than in controls (72-6 ± 8-7 mU/mg protein) (p < 0-05). Intracellular localisation studies showed that the decrease was specific to the cytosolic component of the enzyme, whose activity in the mitochondria was normal.

Thus, chronic ethanol abuse is associated with a reduced hepatic activity of the enzyme catalysing the removal of its more toxic oxidation product—acetaldehyde. This may explain the higher blood levels of acetaldehyde in alcoholics, and has important implications in understanding the pathogenesis of alcoholic liver injury.

**Vitamin D metabolism in primary biliary cirrhosis and extrahepatic obstructive jaundice**

R. T. JUNG, M. DAVIE, P. SIKLOS, T. M. CHALMERS, J. O. HUNTER, AND D. E. M. LAWSON (Addenbrooke’s Hospital and MRC Dunn Nutrition Unit, Cambridge) Osteomalacia is frequently observed in cholestatic liver disease. To study the importance of bile duct obstruction in vitamin D metabolism, we investigated six cases of acute extrahepatic obstructive jaundice (OJ) and eight cases of primary biliary cirrhosis (PBC) (three supplemented with vitamin D).

Plasma 25-hydroxy vitamin D (25-OHD) was low in PBC (unsupplemented) (5-2 ± 4-5 ng/ml) (p < 0-05 of normal) but normal in OJ (8-4 ± 4-9). No case of PBC showed histological osteomalacia. Dietary intake of vitamin D in PBC was low (40 ± 24 IU), but response to ultraviolet light was normal. Plasma 25-OHD-binding protein (Gc) was low in PBC (223 ± 54 µg/ml) and OJ (235 ± 17 nr 300-550 µg/ml). This reflects low serum albumin, which correlates with Gc (r = 0-78, p < 0-001).

3H4 half-life in OJ was normal but longer in PBC in contrast to the short half-life in alcoholic cirrhosis (p < 0-05).

All OJ patients and five with PBC had normal 4H25-OHD production. Three with PBC (two supplemented, one after UV light) produced less 4H25-OHD than expected.

Urinary 4H after 4H4 correlated with serum bilirubin (r = 0-84, p < 0-02). Preliminary work suggests that this is not derived from 25-OHD but from other vitamin D metabolites.

Low 25-OHD results from poor intake, inadequate UV exposure, and possibly urinary vitamin D wastage. 25-hydroxyla- tion is normal in OJ and most PBC.

**Impromidine (SK & F 9267)—a highly specific agonist for histamine H2 receptors**

R. H. HUNT, J. A. BILLINGS, JANE G. MILLS, W. L. BURLAND, AND G. J. MILTON-THOMPSON (Royal Naval Hospital, Haslar, and The Research Institute, Smith Kline & French Laboratories Ltd, Welwyn Garden City) Impromidine is a potent and specific histamine H2-receptor agonist in animals and in vitro.1

We have studied the gastric secretory response to impromidine in healthy male volunteers using the phenol red correction technique.2 A 60 minute intravenous infusion of impromidine 10 µg kg⁻¹ h⁻¹ was compared with pentagastrin 6 µg kg⁻¹ h⁻¹ and histamine acid phosphate 40 µg kg⁻¹ h⁻¹ intravenously in 11 subjects. Comparisons were also made between
Glucose and fat introduced into the stomach or into the duodenum did not inhibit gastric emptying (distilled water, \( T_{1/2} < 3 \) min; glucose and fat, \( T_{1/2} < 3 \) min). However, both fat and glucose instilled separately into the jejenum did inhibit gastric emptying (distilled water, \( T_{1/2} < 3 \) min; fat, \( T_{1/2} > 60 \) min; glucose, \( T_{1/2} > 200 \) min).

The results show that in dogs the braking 'receptors' lie in the small intestine, distal to the duodenojejunal junction, and that there is no braking mechanism in the duodenum.

### Gastric cancer detection in gastric ulcer disease

R. A. MOUNTFORD, P. BROWN, P. R. SALMON, C. S. NEUMANN, AND A. E. READ (University Department of Medicine, Bristol Royal Infirmary, Bristol) In an attempt to determine which clinical and diagnostic features might increase the suspicion of malignancy in patients with gastric ulceration, a retrospective survey of all patients with gastric ulcer diagnosed endoscopically in our unit over a three year period has been performed. Two-hundred-and-sixty-five patients with gastric ulcer have been studied with an average length of follow-up of two years, and of these, 37 (14\%) proved malignant. Presenting complaints of anorexia, weight loss, nausea and vomiting, and multiple (>3) symptoms were significantly more common in the malignant group, but ulcer site and co-existing duodenal ulceration were unhelpful in determining the status of an ulcer. Larger (>1cm) ulcers had a significantly higher risk of malignancy than small ulcers. If a definitive statement on the nature of an ulcer was made, then radiology was unreliable in distinguishing benign from malignant ulcers (14\% false positives; 40\% false negatives). An equivocal opinion on the nature of an ulcer was common at both endoscopy and radiology, especially if the ulcer was benign (endoscopy 56\%, radiology 49\%). Three cases of superficial gastric carcinoma were detected and are the major reason for advocating repeated endoscopy and biopsy of all ulcers until complete healing is achieved.

### Effect of short- and long-term cimetidine on histological duodenitis and gastritis

H. M. GILMOUR, J. A. H. FORREST, MARY R. BETTES, R. F. A. LOGAN, AND R. C. HEADING (Department of Pathology and University Department of Therapeutics and Clinical Pharmacology, The Royal Infirmary, Edinburgh) Patients with endoscopic duodenal ulceration were treated with cimetidine (1 or 2 g/day) for four or eight weeks until there was endoscopic evidence of ulcer healing and then with 600 mg bd for six months. Before and after each period of treatment, multiple endoscopic biopsies were taken from the duodenum, gastric body, and antrum. Histological grading of duodenitis and gastritis was based on the criteria of Whitehead.

Over the initial four- or eight-week period, the most severe histological duodenitis in each patient was unchanged in 16, improved in seven and increased in three. Antral gastritis increased in all patients (n = 6), no change occurring in body mucosa. Over the six-month maintenance period, six patients showed no change in duodenitis, 15 improved, and 13 deteriorated. During this period, no statistically significant changes occurred in body or antral gastritis (n = 15). The degree of histological duodenitis before full-dose treatment or at entry to the 600 mg bd period was of no value in predicting those patients who would take more than four weeks of full-dose treatment to heal their ulcers or who would relapse during maintenance therapy.

The results demonstrate that gastritis and duodenitis associated with chronic duodenal ulceration are unaffected by cimetidine therapy.

### Cimetidine treatment in chronic and acute forms of Zollinger-Ellison syndrome (ZES)

S. BONFILS, M. MIGNON, AND J. GRATTON (Unité de Recherches de Gastroentérologie Hôpital Bichat, Paris, France) Thirteen cases of ZES were treated with cimetidine. This population could be divided into: (1) chronic forms, mostly presenting as a common duodenal ulcer, (2) acute forms resulting in critical problems requiring intensive medical care.

Among the seven chronic ZES cases, cimetidine treatment was unsuccessful in two; satisfactory clinical control was
obtained in three others, but gastrinoma excision was the final treatment; cimetidine treatment has been prolonged for more than 15 months in the last two cases. If in this condition acute pharmacological secretory inhibition was constantly obtained, therapeutic efficiency criteria are not sensitive enough to feel secure in the patient's long-term follow-up. Total gastroectomy is still a valuable alternative if gastrinoma excision is not possible.

Out of the six acute ZES cases, four were treated by addition of pirenzepin (0.5 mg kg⁻¹ tid, im) to cimetidine infusion (2-4 mg/day) resulting in an increased anti-secretory activity. However, total gastroectomy was the final outcome of every case, with one immediate postoperative death.

In conclusion, cimetidine in ZES management, although capable of inducing ulcer healing, disappearance of diarrhoea and dramatic secretory inhibition, is still challenged by surgery which allows either complete cure of the gastrinoma, or definitive suppression of the secretory virulence.

Reduction by selective gastric vagotomy and by proximal gastric vagotomy of the pancreatic-polypeptide response to food and insulin hypoglycaemia

T. W. SCHWARTZ, N. A. LØVAGREN, J. POUISON, AND E. AMDRUP (introduced by J. F. REHFELD) (Institute of Medical Biochemistry and Department of Surgical Gastroenterology L. University of Aarhus, Denmark) The initial pancreatic-polypeptide (PP) response to food is abolished by truncal vagotomy and the secondary prolonged response is significantly reduced. We have studied the PP secretion before and three months after two types of selective gastric vagotomy. The PP response to food was reduced by proximal gastric vagotomy PGV; integrated initial response 30-60 min 77 (47-103) % of preoperative value, secondary response 30-120 min: 66 (47-98) %, median and interquartile range, N = 15.

Both the initial and the secondary PP response to food were greatly reduced by selective gastric vagotomy (SGV); integrated initial response: 16 (8-46) % of preoperative value, secondary response: 24 (8-42) %, N = 23. No rapid increase (5-10 min) in PP concentrations were found in 10 out of 23 patients after SGV, but in only one out of 15 patients after PGV.

The PP response to insulin hypoglycaemia is abolished by truncal vagotomy. After SGV or PGV a positive correlation was found between the reduced, initial PP response to food and the integrated PP response to insulin hypoglycaemia, rₚ = 0.93, p < 0.01, N = 9. A weaker correlation was found between the secondary PP response to food and to hypoglycaemia, rₚ = 0.63, p < 0.05. Assuming that insulin hypoglycaemia is a central stimulus, this study indicates that the vagal innervation to the pancreas is severely injured during SGV but generally spared during PGV.

References

SMALL AND LARGE BOWEL/LIVER AND BILIARY

Does abnormal gastric mucosal permeability contribute to poor results after peptic ulcer surgery?

M. J. GOUGH, LINDA WOODHOUSE, C. S. HUMPHREY, AND G. R. GILES (University Department of Surgery, St James's University Hospital, Leeds) Some patients do badly after peptic ulcer surgery, possibly due to bile reflux, abnormal gastric emptying, or gastric mucosal damage. Gastric mucosal permeability assessed by back diffusion of lithium chloride may reflect mucosal damage. This study measured lithium fluxes in 18 patients with peptic ulcer, 12 patients with recurrent ulcer post-vagotomy, and 12 patients with dumping, bile vomiting, or non-specific pain after peptic ulcer surgery. Simultaneously bile reflux under basal conditions, peak acid output to pentagastrin, and liquid test meal emptying times were measured.

Pre-operative lithium fluxes were significantly lower (0.121 mmol Li⁻⁻ ± 0.017/15 min) than in patients with recurrent ulcer (0.177 mmol Li⁻⁻ ± 0.022) and patients with a poor surgical result (0.194 mmol Li⁻⁻ ± 0.023) (p < 0.05). Bile reflux was absent in preoperative patients but present in patients with recurrent ulcer (0.22 mmol/ h ± 0.16) and symptomatic patients (0.36 mmol/h ± 0.13). However, there was no significant correlation between the degree of bile reflux and back diffusion of lithium in any group.

Test meal emptying times in recurrent ulcer patients and symptomatic patients was significantly faster than in pre-operative patients (p < 0.025). These results did not correlate with lithium fluxes, though postoperative bile reflux was associated with more rapid gastric emptying.

Gastric mucosal permeability measured by lithium back diffusion is increased in patients with poor surgical results. These differences are not directly related to the degree of bile reflux, nor changes in gastric emptying or acid secretion.

Reference

Functional classification of intestinal endocrine cells

A. M. J. BUCHAN AND J. M. POLAK (Department of Histochemistry, Royal Postgraduate Medical School, Hammersmith Hospital, London) Many biologically active gut peptides are produced by mucosal endocrine cells. Accurate identification of the cell types is essential as recent results indicate.

We have two groups of motilin antisera, one directed to the C-terminal, the other to the whole molecule. The antisera to the whole molecule stain two cell types: enterochromaffin with large (350 nm), polymorphic, argentaflin granules and cells with small (180 nm), round, electrondense, non-argentaflin granules. This indicates either a cycle of cellular motilin production or that there are at least two motilin-like peptides.

The availability of neurotensin antibodies allowed the identification of a previously unknown ileal cell type with large (300 nm), round, electrondense granules. Using antibodies to glicentin (specific for gut glucagon-like immunoreactivity), we have shown that (in man) glicentin is produced by cells with small (190 nm) round, electrondense granules.

Use of highly specific antibodies combined with the semithin/thin technique has shown the inaccuracy of previous cell
classifications by morphological criteria. For example, the D₁ cell type has proved to be a heterogeneous group of cells producing intestinal gastrin, motilin-like immunoreactivity, and glicentin.

A functional classification of peptide-producing cells, stressing the product rather than morphological appearance, is therefore advisable in view of the increasing complexity of gut endocrinology.

Comparative study of long-term systemic and topical glucocorticoids on the rat small intestine

J. SCOTT, R. M. BATT, AND T. J. PETERS (introduced by V. S. Chadwick) (Royal Postgraduate Medical School, London)

Short-term prednisolone selectively enhances the digestive-absorptive capacity of the rat jejunum, without altering morphology or enterocyte kinetics. In the present study the effect of long-term soluble prednisolone-21-phosphate and topical betamethasone-17-valerate has been examined. Adult male Wistar rats were fed either prednisolone (0-75 mg kg⁻¹ day⁻¹) or betamethasone (0-06 mg kg⁻¹ day⁻¹) for 28 days or were pair-fed as controls. Jejunal enterocytes were isolated, brush border marker enzymes assayed, and activity expressed per enterocyte and per cm of intestine. D-galactose absorption was measured using a recirculation perfusion technique and a non-absorbable (¹⁴C)-polyethylene glycol marker. Enterocyte kinetics were studied using (3H)-methylthymidine 1.

Both prednisolone and betamethasone increased brush border enzyme activities and D-galactose absorption per enterocyte. With prednisolone this resulted in significantly enhanced brush border enzyme activities and D-galactose absorption per cm jejunum. In contrast betamethasone produced marked mucosal atrophy and consequently no net alteration in either brush border enzyme activity or D-galactose absorption per length of intestine.

Thus prednisolone produces a sustained increase in the digestive-absorptive capacity of the jejunum, which may be of clinical value. Betamethasone-17-valerate, however, causes marked atrophy and thus is unlikely to be useful in intestinal disease; it may be contraindicated where there is pre-existing mucosal injury.

Adaptation of the shortened gut: differential response in functioning and isolated bowel

R. C. N. WILLIAMSON, F. L. R. BAUER, AND R. A. MALT (Department of Surgery, University of Bristol, United Kingdom, and Surgical Services, Massachusetts General Hospital, Boston, USA) Evidence supporting hormonal control of intestinal adaptation includes the transmission of an enterotropic factor between parabiotic rats and the greater intensity of distal hyperplasia following jejunal resection as opposed to jejunal bypass. Humoral regulation of intestinal growth was further tested in rats (N=80) submitted to 50% proximal small bowel resection, with exclusion of the upper half of the remaining ileum as a Thiry-Vella fistula (TVF). Other groups had creation of an ileal TVF alone (sham resection) or simple laparotomy (control). Mucosal scrapings from 5-cm intestinal segments were analysed for nucleic acid content and [H]TdR-labelled radioactivity.

Compared with controls at 48 hours, jejunal resection increased RNA and DNA by 15% (p<0.05) in duodenum, by 18-21% (p<0.01) in defunctioned (upper) ileum and by 27-35% (p<0.001) in functioning (lower) ileum. Compared with sham resection, radioactivity in the TVF was 36% higher (p<0.02). One week after resection, nucleic acids remained 20-38% higher than either controls or sham resection in the duodenum and 16-33% higher in the ileal TVF (p<0.05 to 0.001); but the greatest increases (27-86%) again occurred in the functioning lower ileal segment.

Although luminal factors contribute to mucosal adaptation in bowel exposed to the nutrient stream, they cannot explain compensatory hyperplasia found either in isolated bowel or in bowel proximal to the site of resection.

References


Colon adenomas—a colonoscopic appraisal

C. B. WILLIAMS, P. E. GILLESPIE, B. C. MORSON, T. CHAMBERS, AND J. C. CHUAN (St Mark’s Hospital, London) A colonoscopic survey of 620 patients with 1049 colon adenomas shows a predominantly left-sided distribution (77%). Of these lesions 97% were amenable to endoscopic removal or ablation. Sixty per cent of patients presented with rectal bleeding as their major symptom. Forty-eight per cent of adenomas in our series were less than 1-0 cm in diameter. Of the larger adenomas (>2-0 cm in diameter), 66% were situated in the sigmoid colon, and of those with invasive malignancy (4-8% of the total) an even higher percentage (94%) were in the sigmoid and low descending colon. With increasing polyp size, there was a greater predominance of villous elements and this was associated with a higher risk of malignant change than the more frequent and generally smaller tubular adenoma. Local colonoscopic excision alone is sufficient treatment for adenomas with malignant change, unless they are poorly differentiated histologically, providing adequate resection is demonstrated. Twenty-eight patients treated in this way were alive without recurrence at periods from six to 62 months. Although 65% of patients had only one adenoma, and 90% three or less, there is a risk of developing further benign and malignant colon neoplasms and careful follow-up is required.

Dietary fibre, Vivonex, cholesterol and experimental colon cancer

J. P. CRUSE, M. R. LEWIN, G. P. FERULANO, AND C. G. CLARK (Surgical Unit, University College Hospital Medical School, London) Epidemiological studies implicate low-fibre, high-fat diets in the aetiology of colon cancer. We have tested aspects of this hypothesis in the dimethylhydrazine (DMH)-induced rat colon cancer model.

Five groups of 20 rats were allocated dietary regimens as follows: high fibre (20% w/w); standard fibre (3% w/w); low fibre (<1-0 w/w); Vivonex (elemental, no-residue, liquid diet), and Vivonex plus cholesterol (100 mg/l). Within each group, half the animals received carcinogen (DMH, 40 mg kg⁻¹ bw⁻¹ wk⁻¹, subcutaneously, for 13 weeks) and half received saline subcutaneously as controls. Animals were weighed weekly, inspected daily for
tumour presentation, isolated when moribund, killed when deemed terminal, and subjected to necropsy. At 44 weeks, all controls were alive, while mortality in the fibre groups was 60%, 80%, and 60% respectively with no difference in latent period, incidence of tumours or metastases. However, in the Vivonex group, mortality was significantly reduced to 10% (p < 0.01) with greatly increased latent period. The 'protective' effect of Vivonex was abolished by the addition of cholestrol, this group having a 60% mortality and similar tumour parameters to the fibre groups.

Manipulation of dietary fibre in this model did not influence carcinogenesis. Vivonex however exerted a protective effect which was nullified by cholestrol, implicating dietary fat as a potent co-carcinogen.

Vitamin D prophylaxis and osteomalacia in chronic cholestasis

JULIET E. COMPSTON, J. CROWE, I. WELLS, L. W. L. HORTON, D. HIRST, A. L. MERRETT, J. S. WOODHEAD, AND R. WILLIAMS (Gastrointestinal Research Unit, Rayne Institute, and Department of Surgical Pathology, St Thomas' Hospital, London; the Liver Unit and Departments of Chemical Pathology and Radiology, King's College Hospital, London; and the Department of Medical Biochemistry, The Welsh National School of Medicine, Cardiff, Wales) The prevalence of histological osteomalacia was investigated in 32 patients with chronic cholestatic liver disease, 17 of whom were receiving high doses of parenteral vitamin D. Undecalcified sections of transiliac biopsy specimens were quantitatively assessed. Plasma 25-hydroxyvitamin D was measured by a competitive protein-binding assay, and plasma parathyroid hormone by radioimmunometric assay.

Four patients had histological osteomalacia. In two, who were receiving prophylactic vitamin D, the bone disease was mild and may have been healing, while in the remaining two, who were not receiving vitamin D, more severe osteomalacia was present. Clinical symptoms, radiology, and serum calcium and phosphate concentrations were not reliable indicators of bone disease, and the development of osteomalacia was unrelated to the duration or severity of liver disease.

Plasma 25-hydroxyvitamin D levels were normal in all patients receiving vitamin D (mean ± SD, 45.9 ± 16.8 nmol/l) but were low in many untreated patients (22.9 ± 15.2 nmol/l) being lowest in the two with severe bone disease. Plasma parathyroid hormone concentration was increased in only one patient.

It is concluded that vitamin D deficiency is common in untreated patients with chronic cholestasis, and some may develop severe osteomalacia. High-dose parenteral vitamin D therapy is usually effective in preventing osteomalacia.

Reversible focal seizures as a manifestation of chronic portosystemic encephalopathy

N. E. F. CARTLIDGE, D. BATES, A. ANDERSON, AND O. JAMES (Department of Neurology, Victoria Infirmary, and Department of Medicine (Geriatrics), Freeman Hospital, Newcastle upon Tyne) The classical clinical features of chronic hepatic portosystemic encephalopathy (PSE), known for 2300 years, were definitively described by Adams and Foley. In current texts on liver disease and neurology, little or no mention is made of focal (Jacksonian) seizures, myoclonus, or even generalised epilepsy as features of chronic PSE. Epilepsy is well recognised in acute PSE.

In a current neurological study of hepatic coma, 50 patients with coma or severe pre-coma associated with chronic liver disease have been studied. In four, generalised epilepsy was a prominent feature of deteriorating encephalopathy. All four, together with a fifth patient, also had well defined, frequently repeated, Jacksonian fits; in two, myoclonus was also a mark of worsening encephalopathy. All five subjects had biopsy-proven alcoholic cirrhosis (one with portocaval shunt) but no recent alcohol ingestion. Subsequent post mortem brain histology revealed no focal abnormality in the cerebral cortex of three patients, a fourth died of a stroke, the fifth patient is still alive.

We suggest that (1) chronic PSE may produce focal neurological signs with no underlying anatomical lesion, and (2) careful neurological assessment and observation of patients with relapsing PSE may reveal these features more frequently than has hitherto been realised.

References


The British Society of Gastroenterology

Impaired bacterial opsonisation due to complement deficiency in patients with fulminant hepatic failure

R. J. WYKE, I. A. RAJKOVIC, D. B. A. SILK, AND R. WILLIAMS (Liver Unit, King's College Hospital Medical School, London) Patients in fulminant hepatic failure (FHF) are known to show an increased susceptibility to bacterial infection. We have studied opsonisation, an important humoral factor in most defence to infection, by incubation of E. coli (1 x 10⁹/ml) and normal polymorphonuclear leucocytes (2.5 x 10⁹/ml) with sera diluted 1:25 from 12 patients with FHF in grade IV coma and matched controls. Patient sera killed only 10-5 ± SD 17-9% of the E. coli compared with 93-3 ± 7-6% for control sera (p < 0.001). Cross-over dilution studies showed that defective opsonisation was not related to the presence of toxins but to a deficiency in patients' sera that was corrected by adding 1:160 dilutions of the heat labile component of normal serum. This finding led us to measure the serum levels of complement factors in these patients. Functionally active total haemolytic complement, C₃, alternative pathway factors B and D were all highly significantly (p < 0.001) reduced (irrespective of aetiology or outcome).

Serial studies in all four survivors showed that E. coli opsonisation returned to normal within 16-6 ± SE 6-7 days in parallel with a return to normal of complement factors.

We conclude therefore that patients with FHF have impaired bacterial opsonisation due to complement deficiency, which may explain their increased susceptibility to infection.

References

Intracranial pressure monitoring in fulminant hepatic failure

M. A. Hanid, M. H. Davies, P. J. Mellon, J. J. MacCabe, L. Strunin, D. B. A. Silk, and R. Williams (Liver Unit, King's College Hospital Medical School, London) Cerebral oedema remains one of the commonest causes of death in fulminant hepatic failure (FHF)1,2. The aims of the present study were to monitor intracranial pressure (ICP) in patients with FHF and to investigate the effects on ICP of prophylactic dexamethasone therapy (32 mg intravenously followed by 8 mg four hourly), mannitol therapy (40-100 mg intravenously following a sustained pressure rise > 20 mmHg/h), and polyacylronitrile-membrane haemodialysis.

Subdural pressure transducers were inserted in eight patients with FHF shortly after admission in grade IV coma. Pressure on insertion was 13±0 ± SD 11±4 mmHg. Two patients survived in whom the highest ICP recordings were 47 and 35 mmHg. In these mannitol reversed or arrested ICP rises. Precipitous rises in ICP (>110 mmHg over six to nine hours) were observed in five of the six patients who died. However, mannitol was effective only if given when ICP < 50 mmHg.

Haemodialysis (six periods in eight patients) was associated with a significant increase in ICP (29±3 ± SD 29±1 mmHg over four hours) compared with that observed in the preceding four hours (7±0 ± 6±8, p < 0.05).

We conclude, therefore, that, despite high dose dexamethasone prophylaxis, precipitous rises in ICP still occur in FHF and that mannitol should be given before the pressure exceeds 50 mmHg.

Liver disease in the male homosexual

P. W. N. Keeling, J. Bull, J. E. Banatvala, J. C. Coleman, I. M. Murray-Lyon, and R. P. H. Thompson (Departments of Gastroenterology, Microbiology, and Virology, St Thomas' and Charing Cross Hospitals, London) We have ascertained the prevalence of HBsAg and liver disease among male homosexuals attending two London venereal disease clinics and correlated the histological changes with viral markers.

Routine liver function tests were assessed in HBsAg + ve patients and if persistently abnormal, liver biopsy was recommended. Over three years 1221 homosexuals were assessed: 91 were HBsAg + ve. Of these 91, 15 had normal and 39 abnormal liver function tests, and 37 declined investigation. Of the 39 patients with abnormal tests, 10 had acute type B hepatitis, nine refused further investigation, and 20, all of whom were asymptomatic, underwent liver biopsy. The histological appearances of the specimens showed five with minimal changes, four persistent hepatitis, two chronic lobular hepatitis, seven active chronic hepatitis, and two with active cirrhosis. 'e' antigen was present in all patients with active chronic hepatitis or cirrhosis, but in only half of those with milder liver disease. To date, in two patients 'e' antigen has spontaneously disappeared from the blood.

These results indicate a high prevalence of liver disease among HBsAg + ve male homosexuals, particularly those carrying the 'e' antigen, and suggest that liver disease is more frequent and severe than among HBsAg + ve blood donors.

References


Pyrogastrone was significantly better (p < 0.025), complete remission or persistence of only minimal symptoms being obtained in 89% of patients. Oesophageal ulcer healing was achieved in 100% and complete endoscopic healing or persistence of only minimal inflammation was noted in 95% on Pyrogastrone, compared with 33% (p = 0.02) and 67% (p < 0.05) respectively of controls. Side-effects in both groups were mild and required no treatment. There was no demonstrable relationship between healing, side-effects, and serum carbonoxolone levels. The possible mechanisms of action of carbonoxolone in oesophagitis are discussed. Compared with data from trials of other drugs, the results of this study would suggest that Pyrogastrone is now the most effective agent available for the treatment of relux oesophagitis.

Double-blind trial of cimetidine in the management of resistant peptic oesophageal stricture

R. Fergusson, M. W. Drongfield, and M. Atkinson (General Hospital, Nottingham) Despite conventional medical measures to control gastro-oesophageal reflex, regular dilatation at frequent intervals is required in about a third of patients with peptic oesophageal stricture.

In a randomised double blind trial we have treated 15 such patients with cimetidine 1-6 daily and placebo, each given for a period of six months. The diameter of the stricture and severity of oesophagitis was assessed by endoscopy at 0, two, and six months in each treatment period, and dilatation of the stricture was performed when necessary to relieve dysphagia. Symptoms of dysphagia and gastro-oesophageal reflex were recorded daily on diary cards.

There was significant improvement in oesophagitis as graded endoscopically during cimetidine treatment when compared with placebo. Restricting, as assessed by the degree of dysphagia, the diameter of the stricture measured at endoscopy, and the need for further dilatations was, however, the same in the cimetidine and placebo treatment periods.

We conclude that, when given for six months, cimetidine does diminish oesophagitis but that this is not reflected in a reduction in the need for dilatation.

References

1. Ferguson, R., and Atkinson, M. (1978). Outlook...
Studies on the effects of cimetidine on anterior pituitary hormones; are they clinically relevant?

S. LA BROOY, J. J. MISIEWICZ, G. DELITALA, A. JONES, C. R. W. EDWARDS, G. M. BESSER, W. A. STUBBS, K. G. M. M. ALBERTI (Central Middlesex Hospital, London; St Bartholomew's Hospital, London; University College Hospital, London; Southampton General Hospital, Southampton) Raised serum prolactins and gastrinomastia have been reported on chronic treatment with cimetidine. We have previously shown that circulating prolactin levels remain unchanged in subjects given intravenous cimetidine 100 mg h⁻¹ over four hours. Intravenous bolus doses of up to 400 mg, however, raised serum prolactin and this response was dose dependent.1 However, there are no data relating to prolonged measurements of serum prolactin levels after oral cimetidine.

Fourteen patients with peptic ulcer have been studied. In 10, serum prolactin was measured at 30 minute intervals for 2.5 hours at the end of a month’s treatment with cimetidine 1 g/day. Four other patients were studied during two 12 hour periods, before and after four weeks of cimetidine 1 g/day. Two-hourly blood samples were taken for anterior pituitary hormones, cortisol, insulin, and blood metabolites. Identical meals were eaten on both study days. Analysis of serum prolactin levels in the 10 patients studied after treatment showed no increase above the normal range, nor was there any significant difference between values in the four patients studied before and after cimetidine therapy.

These results suggest that the clinical relevance of the reported hyperprolactinaemia in patients taking cimetidine is doubtful, particularly as prolactin is a stress-related hormone and may be raised nonspecifically.

Reference

Increasing gallstone disease in Gibraltar—a clue to aetiology?

R. H. HUNT (Royal Naval Hospital, Haslar, Gosport, Hampshire) Gallstone disease is common in Europe and the incidence is increasing.1,2

A marked increase has occurred in Gibraltar where cholecystectomy is now five times more common than in Bristol. Between 1963 and 1976 the mean adult population remained 14,060 ± 190 (SE) and gall-bladder operations increased from means of 27 for the first quinquennium to 86 for the last quinquennium. This three-fold increase is linear and highly significant over the time period (r² p < 0.001). These findings are supported by analysis of gall-bladder operations as a proportion of general surgical procedures.

Analysis by age and sex shows a shift to a younger age, although this is not significant and contrasts with other reported studies.

Between 1969 and 1974, 1243 individual patients (8.8% of the adult population) underwent 1812 radiological investigations of the biliary tract. The films of 1024 patients were scrutinised and gallstones seen in 308 (30%) or a non-functioning gall bladder in 326 (32%). Yearly analysis showed a highly significant linear increase in total and positive examinations (r² p < 0.001).

Analysis of food imports and consumption showed no significant changes and the cause of this increase is not clear.

Gut hormone profile in morbid obesity and after jejunooileal bypass

H. S. BESTERMAN, D. L. SARSON, A. M. BLACKBURN, J. CLEARY, T. R. E. PILKINGTON, J. C. GAZET, AND S. R. BLOOM (Royal Postgraduate Medical School, London, St James’ Hospital, London, and the George’s Hospital, London) The role of gut hormone operations in the metabolic disorders of obesity and after bypass is poorly understood. We have therefore investigated the effect of a standard test breakfast (18 g protein, 22 g fat, 66 g carbohydrate, 530 kcalories) on gut hormone release in 19 patients with morbid obesity (225 ± 7% ideal weight) and compared it with 16 age and sex matched normal controls (106 ± 3% ideal weight). In addition, 21 patients were studied between two and 12 months after jejunooileal bypass (181 ± 8% ideal weight). All patients had lost weight post-operatively (28 ± 2 kg).

In obesity we find no gut hormone abnormality corresponding to the augmented blood glucose and insulin responses. After bypass, there is a dramatic five-fold diminution in GIP release, an eight-fold increase in neurotensin release, and a massive 16-fold increase in enteroglucagon release. The striking alteration in the pattern of gut hormone release after jejunooileal bypass provides important new insight into the metabolic changes following this operation.

Team approach to long-term intravenous feeding in gastroenterological patients

J. POWELL-TUCK, THALIA NIELSON, J. FARWELL, AND J. E. LENNARD-JONES (St Mark’s Hospital, London) A system has been developed for administration of intravenous feeding for prolonged periods in general wards. The service is coordinated by a clinician, specialised nurse, and pharmacist. A silicone rubber catheter is introduced under local anaesthesia using the infraclavicular route and creating a skin tunnel. With this technique 22 of 27 treatment periods (mean duration 44 days) have needed only one catheter. Ward care is simplified by the use of three-litre bags containing all nutritional requirements except fat. Each bag is prepared under laminar flow conditions by a pharmacist in a specially designed room. Studies of the solutions we use have shown that the amino acids, glucose, electrolytes, and trace elements are compatible. Vitamins are added to the mixture and intralipid is infused separately as needed.

In 38 treatment periods over a total of 1551 days there was satisfactory weight gain which correlated with gain in fat free mass, assessed from skin-fold measurements (r=0.86), and arm muscle cross-sectional area (r=0.72). Some patients who have learnt to spigot and care for the catheter have left the hospital for periods of up to three days, and two patients have given themselves supplemental infusions regularly by night at home.

Effect of a dietary fibre on gastric emptying in dumpers

D. N. L. RALPHS, O. LAWAETZ, N. J. G.
BROWN, AND A. R. LEEDS (introduced by M. Hobsley) (Departments of Surgical Studies, The Middlesex Hospital and Gastroenterology, The Central Middlesex Hospital, London) Pectin decreases post-prandial glycaemia in normal subjects when added to a carbohydrate meal and also improves symptoms after a glucose drink in patients with the dumping syndrome. 

In this study six patients, who dumped after meals following gastric surgery for duodenal ulceration, were given 150 ml 50% glucose on one occasion and the same meal with an added 10 g pectin on another. Both meals were labelled with 1-5 mCi Indium113m. The symptoms experienced were recorded and serial haematocrit measurements made on venous blood samples. Gastric emptying was monitored using a gamma camera system.

The addition of pectin alleviated the symptoms. The maximum falls in plasma volume, derived from the haematocrit readings, were significantly less in the pectin studies (p = 0.05) and the 

The distribution of the meals within the stomach and the rate of emptying showed different patterns in the two sets of studies.

The results confirm the symptomatic improvement with pectin in dumping subjects in these circumstances. They suggest that the modification in the way in which the stomach handles the pectin meal may be the prime cause of this effect.

References

Barium infusion examination in acute small bowel obstruction

C. G. MARKS AND D. J. NOLAN (Departments of Surgery and Radiology, Radcliffe Infirmary, Oxford) Twenty-three patients who were admitted to hospital over a 21 month period with suspected small bowel obstruction were examined with a barium infusion. The examination was performed by infusing barium through a tube directly into the small intestine and taking radiographs when indicated under screening control.

Mechanical small bowel obstruction was confirmed in 22 patients and the small intestine was shown to be normal in one patient. The level of obstruction was shown in all except one patient, who had a carcinoma of the caecum.

Seven patients were shown to have Crohn's disease of the small intestine but only two required emergency surgery. Six patients had metastatic disease involving the small intestine and they all came to operation. Small bowel obstruction was caused by adhesions in three patients and two were operated on. In the third patient the barium appeared to release adhesions adjacent to a drainage tube. The remaining five patients had miscellaneous lesions: a radiation stricture, femoral hernia, ileostomy twist, ischaemic stricture with perforation, and a malrotation. They all came to operation.

There were no complications associated with the examination or with the subsequent operation.

Reference

Pathogenesis of sepsis after appendicectomy

I. A. DONOVAN, D. ELLIS, D. GATEHOUSE, G. LITTLE, R. GRIMLEY, S. ARMSTEAD, M. R. B. KEIGHLEY, AND C. J. L. STRACHAN (General Hospital, Birmingham; Queen Elizabeth Hospital, Birmingham; Dudley Road Hospital, Birmingham; and Royal Infirmary, Huddersfield) The relative importance of aerobic and anaerobic organisms in the genesis of infection after appendicitis remains uncertain. We therefore designed a prospective randomised trial of single dose prophylaxis to compare an agent effective against anaerobes (clindamycin phosphate) with one effective against aerobes (cefazolin sodium).

Two-hundred-and-fifty patients aged over 12 years entered the trial, there were12 withdrawals. Seventy-two patients received placebo, 81 received 600 mg clindamycin, 85 received 1 g cefazolin given intramuscularly immediately before operation.

Overall wound sepsis rates were placebo 33% clindamycin 17% cefazolin 35% (p < 0.05 clindamycin versus others. Chi-squared Yates correction). In 52 patients with gangrenous or perforated appendicitis overall wound sepsis rates were placebo 78% clindamycin 44% cefazolin 80% (p < 0.05 clindamycin versus others).

Microbiology was obtained in 50 wound infections. Anaerobes were isolated in 60% of placebo, 38% of clindamycin, and 60% of cefazolin infections; aerobes from 90% placebo, 100% clindamycin, and 64% cefazolin infection. Cefazolin significantly reduced the number of aerobic isolates (p < 0.05).

We conclude that an agent active against anaerobes (clindamycin) significantly reduced wound infection, whereas one active against aerobes (cefazolin) did not, and that anaerobic organisms are therefore of much greater importance than aerobic organisms in the pathogenesis of sepsis after appendicectomy.

Trial of high fibre diet or local treatment for patients with haemorrhoids

Y. ARABI, T. MAKURIA, P. BUCHMAN, J. ALEXANDER-WILLIAMS, AND M. R. B. KEIGHLEY (The General Hospital Birmingham) It has been suggested that only patients with piles who have high anal pressures should be treated by procedures which reduce anal pressure because of the risk of prolapse in the remaining patients.

We have therefore undertaken two randomised clinical trials of treatment for patients with piles. Patients with high anal pressure (n = 110) were allocated to treatment by sphincterotomy (LSS), anal dilatation (MDA), or high fibre diet (diet). Patients with low pressure (n = 111) were allocated to rubber band ligation (RBL), cryosurgery (C), or diet. A symptomatic review and measurement of anal pressure were repeated one and four months after treatment.

In the high pressure group: LSS, MDA, and diet were equally effective and relieved symptoms in 85-92% of patients at four months. There was a 9% reduction in anal pressure by all forms of therapy. In the low pressure group: diet improved only 50% at four months compared with 83% after C and 87% by RBL. There were more complications and an increase in time off work after C than RBL.

These data indicate that diet is effective and has economic advantages over LSS and MDA for patients with high anal pressure, but that RBL is preferable for patients with low anal pressure.

References
Excision or resection for carcinoma of the middle third of the rectum?

R. J. Nicholls, Jean K. Ritchie, Jane Wadsworth, and A. G. Parks (St Mark's Hospital, London) Resection with anastomosis is being used increasingly for carcinoma of the middle third of the rectum, although it is not known if this is as curative as total rectal excision for tumours in this site. More advanced and anaplastic tumours tend to be treated by excision: overall survival rates are not comparable therefore.

Between 1963 and 1972 at St Mark's Hospital, 199 patients underwent potentially curative operations (excision 112, resection 87) for a single adenocarcinoma at \( > 8 \) cm < 12 cm from the anal verge.

Using single pathological variables, the number of deaths due to carcinoma or unknown cause within five years was not significantly different for patients with Dukes' B or average grade tumours after either type of operation. However, patients with Dukes' C tumours fared significantly better after resection.

With two variables, there was no significant difference in five year survival for Dukes' B or C tumours of average grade malignancy after excision or resection.

When the extent of local spread was added as a third variable, a significantly improved survival after resection was found in two subgroups.

These results suggest that resection is as curative as excision for middle-third rectal carcinoma.

Patterns of change in carcinoembryonic antigen (CEA) levels in patients developing recurrent colorectal cancer

C. B. Wood, R. W. Burt, J. G. Ratcliffe, A. J. H. Malcolm, and L. H. Blumgart (University Department of Surgery, Royal Infirmary, Glasgow) Serial CEA estimations were performed in 199 patients after apparently curative surgery for colorectal cancer. In a follow-up period of 15-51 months, 41 patients had two consecutive raised CEA levels (> 25 µg/l). No tumour recurrence was detected in five (12%), and clinical detection preceded raised CEA levels in one (2.4%). CEA levels rose concurrently with, or before, detection of recurrence in the remaining 35 patients (85%). Raised CEA levels preceded detection of recurrence in 32 patients (78%) by two to 28 months (median = four months).

Two patterns of rises in CEA were observed. A slow rise, with levels not exceeding 75 µg/l within 12 months of the first CEA rise, were seen in 15 patients. Of these five have died (33%). In 21 patients CEA levels rose to > 100 µg/l within six months of the first raised level being recorded. Of these 17 (81%) have died. Thus serial CEA assays will allow early detection of recurrent colorectal cancer. The rate of CEA rise may have prognostic significance.

Clinical trial to compare manual dilatation of the anus and lateral subcutaneous sphincterotomy for anal fissure

Y. Arabi, T. Makuria, P. Buchmann, J. Alexander-Williams, and M. R. B. Keighley (The General Hospital, Birmingham) Anal fissures are associated with increased activity of the internal anal sphincter. Manual dilatation (MDA) gives good symptomatic relief but requires a general anaesthetic. Sphincterotomy (LSS) is an alternative technique having the advantage that it may be performed under local anaesthesia.

A prospective randomised trial has compared MDA with LSS in 152 consecutive patients with anal fissures (LSS: n = 75, MDA: n = 77). Anal pressures have been measured before, at four and 12 months after treatment. The incidence of complications, time off work, and a symptomatic assessment were also recorded.

Complications of pain and bleeding occurred in two patients after LSS compared with nine after MDA. Within three days of LSS 87% returned to work compared with only 56% after MDA (\( p < 0.01 \)). At four months there were three patients after LSS and four patients after MDA who developed recurrent fissures. At 12 months four more patients developed recurrent fissure after LSS. Compared with the preoperative pressures there was a sustained reduction at four and 12 months but the percentage reduction was greater after MDA (19%) than after LSS (8%).

These results indicate that LSS has less morbidity and potential economic advantages over MDA but the long-term results of MDA are slightly better than LSS.

The British Society of Gastroenterology

Gut hormone profile in inflammatory bowel disease

H. S. Besterman, S. R. Bloom, N. D. Christophides, C. N. Mallison, A. Peri, and R. Modigliani (Royal Postgraduate Medical School, London; Lewisham Hospital, London; Ospedale Mauriziano, Turin, Italy; and Hôpital St Lazare, Paris, France) We have previously reported characteristic abnormalities in gut hormone release in certain well-defined conditions affecting the alimentary tract—for example, coeliac disease and acute tropical sprue. No previous information has been reported on gut hormones in inflammatory bowel disease. We have, therefore, investigated the gut hormone response to standard test breakfast (530 Kcal) in 14 patients with Crohn's disease, in 24 patients with ulcerative colitis and compared this with 14 age and sex-matched normal subjects. Patients with ulcerative colitis had significantly raised basal and peak gastrin levels (11.8 ± 1.7, 50 ± 8 pmol/l) compared to normal subjects (5.4 ± 0.6, 25.0 ± 7.1, \( p < 0.001 \), \( p < 0.02 \)) and also to patients with Crohn's disease (7.3 ± 1, 21.4 ± 5.9, \( p < 0.05 \), \( p < 0.01 \)). In contrast, basal levels of motilin were raised in both the ulcerative colitis group (141 ± 23 pmol/l) and the Crohn's disease group (157 ± 35) compared to normal subjects (74 ± 15, \( p < 0.05 \) for both). The three hour incremental response of enteroglucagon was greater in the Crohn's disease patients (6.2 ± 1.3 nmol/l) compared both to normal subjects (1.7 ± 0.5 nmol/l, \( p < 0.005 \)) and to patients with ulcerative colitis (3.0 ± 0.5, \( p < 0.05 \)). The release of pancreatic polypeptide and insulin was, however, normal in both groups.

We therefore find that there is a significant difference in the patterns of gut hormone release between Crohn's disease and ulcerative colitis and that these are markedly different from those previously reported for other gut diseases.

References

Prostaglandin synthetase activity in acute ulcerative colitis: the effects of treatment with sulphasalazine, codeine phosphate and prednisolone

D. J. DAWSON, P. R. SMITH, AND C. H. J. SWAN (Department of Gastroenterology, North Staffordshire Hospital Centre, Stoke-on-Trent) Prostaglandins (PGs) have been implicated in the pathogenesis of diarrhoea in disease states. In active ulcerative colitis, faeces contain high levels of PG-like material, and metabolites are excreted in the urine. We have previously shown raised PG synthetase activities in rectal biopsies of ulcerative colitis.

Seven patients with active ulcerative colitis were treated with conventional therapy and rectal biopsies taken at 0, two and four weeks treatment. Rectal PG synthetase activities were assayed by a radiometric method and were shown to fall significantly with treatment (p < 0.001 for difference at 0 and four weeks).

In vitro studies using affected colon from an acute colitic undergoing panproctocolectomy and uninvolving colon from a patient with polyposis coli have shown that sulphasalazine is a potent inhibitor of PG biosynthesis in mucosal homogenates, whereas prednisolone and codeine phosphate are ineffective. Indomethacin, was even more potent than sulphasalazine. Percentage inhibition was similar for normal and colitic mucosa, although absolute values of PG biosynthesis were increased in colitics.

It is shown that prostaglandin synthetase activity is increased in the mucosa of ulcerative colitis during acute attacks and falls during conventional therapy. One of the effects of sulphasalazine may be to inhibit PG biosynthesis, and a therapeutic role for other PG synthetase inhibitors is suggested.

Bacteria, prostaglandins, and ulcerative colitis

M. J. HUDSON, M. J. HILL, S. R. GOULD, AND J. LENNARD-JONES (Bacterial Metabolism Research Laboratory, Collindale, London, and St Mark's Hospital, London) The faeces of patients with acute colitis have been shown to contain high levels of prostaglandins (PGs) and treatment with sulphasalazine (SASP) is paralleled by a fall in PGs to normal low levels. An increased in vitro synthesis of PGs by colonic mucusal biopsies from acute colitics compared to controls and SASP-treated colitics has also been reported.

We have examined the ability of isolates of the intestinal microflora to synthesise PGs from arachidonic acid (AA), a precursor of PGs present in faeces. Mixed cultures of the predominant flora from colitics and controls were grown separately in a complex medium with AA (100 μg/ml). Bacterial pellets, disrupted by ultrasonication or EDTA-toluene treatment were found to contain between 25 and 4500 ng/g PG when assayed by both bioassay and radioimmunoassay. The ratio of PGE2 to PGF2α was approximately 3 to 1, a similar ratio to that found for faecal PGs in colitics. Preliminary qualitative studies using thin-layer chromatography of bacterial PGs produced from 14C-AA suggest that Bacteroides spp. are particularly active in PGE2 production, and that SASP is able to inhibit synthesis. Studies are continuing to investigate the factors controlling bacterial PG synthesis in vitro, the ecology of these bacteria and their role in the pathogenesis of the disease.

References


Immunohisto- and ultracytochemical observations on the early lesion in ulcerative colitis

JAN-OLAF GEBBERS AND HERWART F. OTTO (introduced by D. P. Jewell) (The Royal Free Hospital, London Institute of Pathology, University of Hamburg, Hamburg, W. Germany) Biopsies from 21 young patients with ulcerative colitis in an active state, who were under no treatment with corticosteroids, have been studied by the indirect immunoperoxidase method demonstrating IgA, IgG, IgM and Clq, C3. Parallel electron microscopic observations were carried out in 12 of these cases.

A striking deviation from the normal local lg-cell class pattern was found, resulting in a 30-fold increase of IgG-cells. Abundant extracellular lG occurred, which was released by a large number of necrotic IgG-cells. IgG aggregates were bound to the basement membrane of the surface epithelium, where activated complement (Clq, C3) could also be demonstrated. Simultaneously granulocytes infiltrated the surface epithelium forming microabscesses where IgG, Clq, and C3 are detectable as well.

Electronmicroscopically the infiltrating granulocytes were found to be in a state of degranulation and disintegration and ultracytochemically a release of their lysosomal peroxidase into the interstices was detectable near the basement membrane. In the vicinity of these granulocytes micro-ulcerations were seen.

The association of IgG and activated complement in the active state suggests a local antigen-antibody reaction. The early lesion is probably not only caused by activated complement but also granulocytic mediated as a consequence of a 'frustrated phagocytosis' of membrane-associated immune complexes.

New mast cell stabilising compound in the treatment of ulcerative colitis

P. S. DAVIES AND J. RHODES (Department of Gastroenterology, University Hospital of Wales, Cardiff) Sulphasalazine is the standard treatment for maintaining clinical remission in ulcerative colitis. Some patients are unable to tolerate the compound and attempts have been made to find alternatives. A mast cell stabiliser, disodium cromoglycate, is of some clinical value in this situation. We have examined a new mast cell stabiliser PRD-92 (Boehringer), which is well absorbed, and have compared it with sulphasalazine in 44 patients during remission with ulcerative colitis using a double-blind study. Twenty-two patients took active PRD and placebo sulphasalazine; two of these could not tolerate the new drug and were withdrawn after less than a week's treatment. Twelve of the 20 patients continued in remission for the six-month period of the trial (relapse rate 40%); assessments were based on clinical symptoms, sigmoidoscopy, and rectal histology. Twenty-two patients were given active sulphasalazine and placebo PRD; 20 continued in remission for six months (9% relapse). We conclude that sulphasalazine maintains clinical remission in ulcerative colitis, while PRD—like other mast cell stabilisers—has a relatively weak effect in this clinical situation.
Sphincter on the ileum: mucosal proctectomy, colectomy, and ileo-anal anastomosis for ulcerative colitis

D. JOHNSTON AND N. S. WILLIAMS (University Department of Surgery, The General Infirmary at Leeds) Removal of the anal canal and anal sphincters in patients with ulcerative colitis (UC) is wasteful, because these structures are usually normal. Also, as the disease is primarily mucosal, the rectal muscle is also worth preserving. Provided that the sphincteric apparatus (including puborectalis and levators) is preserved, patients remain continent even after complete excision of the rectum. Complete proctocolectomy, in contrast, may produce impotence, bladder dysfunction, and psychological upset due to the permanent ileostomy.

An alternative approach is to remove the disease by means of subtotal colectomy and mucosal proctectomy, ileum being drawn through the tube of rectal muscle to be Anastomosed just above the anus. In a pilot study, we did this in three young men. Since dissection is endorectal, there is no danger to the pelvic parasympathetic nerves.

All three patients are continent during the day. One is incontinent at night. The frequency of bowel action ranges from seven to 12 per day.

This procedure might be a useful alternative to the reservoir ileostomy.

References

VIP nerves in Crohn’s disease

A. E. BISHOP, J. M. POLAK, M. G. BRYANT, AND S. R. BLOOM (Departments of Histology and Medicine, Royal Postgraduate Medical School, London) Abnormalities of autonomic nerves are known to exist in Crohn’s disease. As VIP nerves form an important part of the autonomic nervous system a combined immunocytochemistry and radioimmunoassay study of their involvement in Crohn’s disease was undertaken.

Surgical specimens were removed from nine patients with Crohn’s disease. Samples were taken from regions of maximal pathology and from proximal and distal areas. Control tissue was obtained from 16 patients with carcinomas and sampled from the following areas: (1) macroscopically normal; (2) distended with no hypertrophy; (3) grossly hypertrophied.

The controls had the normal VIP nerve pattern of fine fibres running through the muscle layers and forming meshes in the submucosa. In groups 1 and 2 the myenteric plexuses were normal in appearance and VIP innervation. The plexuses in group 3 were distorted but contained normal VIP innervation. The nerves in the diseased samples were increased in number and degree of immunostaining with distended fibres and disorganised, densely packed meshes and plexuses. Radioimmunoassay of gut extracts showed increased VIP concentration in the Crohn’s tissues (243 ± 51 pmol/g) compared with control tissues (121 ± 16 pmol/g) (p < 0.05).

These results suggest that there is a remarkable involvement of VIP innervation in the pathology of Crohn’s disease and that further investigation is important to ascertain whether these changes play any role in aetiology.

Crohn’s disease activity index—is it useful?

A. S. MEE, D. J. BROWN, AND D. P. JEWELL (Academic Department of Medicine, Royal Free Hospital, London) Assessment of activity in Crohn’s disease is notoriously difficult. The Crohn’s disease activity index (CDAI) attempts to provide a measure of severity based on objective criteria, allowing a comparison of activity scores between different centres. We have found the CDAI to be cumbersome to use and have therefore compared it with a simple clinical assessment at the time of seeing the patient, the ESR, and the serum level of C-reactive protein.

The CDAI was obtained in 42 consecutive patients. Simultaneously a clinical assessment was made which included general well-being, presence or absence of pain, diarrhoea, and complications. The disease was graded as inactive, mild, moderate, or severe. Blood was taken for ESR and C-reactive protein (measured by Laurell immunoelectrophoresis). Twenty-six per cent of patients had a CDAI of more than 150 and would therefore be regarded as having active disease.

The four methods of assessment were compared using Spearman’s rank correlation coefficients (with mathematical adjustment for tied ranks). There was a highly significant correlation (p < 0.01) between each method of assessment. No one method appeared to be a more sensitive indicator of disease activity.

For multicentre studies of Crohn’s disease, the CDAI provides an objective method of disease assessment but does not appear to be superior to an ESR or C-reactive protein estimation.

Effects of antacids on the absorption of cimetidine

G. BODEMAR, JANE G. MILLS, B. NORLANDER, P. OSBORNE, W. L. BURLAND, AND A. WALAN (University Hospital, Linkoping, Sweden, and The Research Institute, Smith Kline & French Laboratories Ltd, Welwyn Garden City) The absorption of a single oral dose of cimetidine 400 mg taken with and without antacids has been studied after a meal in 11 healthy subjects, and in 18 fasting patients with peptic ulcer disease.

In healthy man 20 ml (or two tablets) antacid was given before and 30, 90, and 150 minutes after cimetidine. Concurrent administration of Aludrox, magnesium trisilicate BPC, Maalox, and Rennies had no effect on the bioavailability of an oral dose of cimetidine. Neutralising capacity was 10, 11, and 25 mmol HCl/10 ml antacid and 15 mmol HCl/tablet, respectively.

In fasting patients concomitant administration of 30 ml of an antacid containing aluminium and magnesium hydroxide (Novalucol, neutralising capacity 35 mmol HCl/10 ml) caused a significant decrease in mean peak blood concentration (p < 0.001) and the mean area under the blood concentration curve was reduced by 22% (p < 0.001). However, no effect was seen when 30 ml Aludrox was given under the same experimental conditions.

Concurrent administration of cimetidine and antacid suspension with a high buffering capacity should be avoided when the patient is fasting, but this is unlikely to occur in practice, as dosage instructions...
for cimetidine recommend that it is taken with or after meals and at bedtime.

Effect of maintenance cimetidine treatment in duodenal ulcer and the eventual outcome after cessation of treatment

M. W. DRONFIELD, A. J. BACHELOR, W. LARKWORTHY, AND M. J. S. LANGMAN (University Department of Therapeutics, City Hospital, Nottingham: and RAF Hospital, Nocton Hall, Lincoln) Forty-two patients with endoscopically diagnosed duodenal ulcer (DU) were studied in a double-blind trial after their ulcers had been healed by cimetidine. Cimetidine was effective in preventing relapse, only five of the 20 patients allocated to cimetidine 400 mg twice daily relapsing during the six months' treatment (cumulative relapse rate, CRR, 25%), compared with 16 of the 22 on placebo treatment (CRR 76%; p < 0.01). The 21 patients who were asymptomatic at the end of the trial had their treatment discontinued and have been followed-up for at least a further eight months in all but five cases. Relapse in these patients was common, particularly in those previously treated with maintenance cimetidine, in whom the CRR rose from 25% to 65% in the eight months after discontinuing the trial, compared with a rise from 76% to 84% in those previously treated with placebo. Thus, the eventual outcome in patients treated with maintenance cimetidine was only slightly better than that in those who had received placebo, and it is likely that, if cimetidine is to be used for DU, the majority of patients will require prolonged if not indefinite maintenance treatment. Until such treatment is shown to be safe and effective, surgery remains the treatment of choice for most patients with severely symptomatic DU.

Adenine arabinoside therapy in hepatitis B antigen positive chronic liver disease

M. F. BASSENDINE, R. G. CHADWICK, E. M. CRAWFORD, H. C. THOMAS, AND S. SHERLOCK (Department of Medicine, Royal Free Hospital, London) Adenine arabinoside (ARA-A) is a synthetic purine nucleoside with activity against DNA viruses. We report the effect of ARA-A on the hepatitis B virus (HBV) in chronic liver disease (CLD).

Four male patients, aged 23-48 years, with biopsy proven HBsAg + ve CLD (duration > six months) were treated. These patients had Dane particles (HBV) in their serum by immune electron microscopy and raised HBV specific DNA polymerase activity (DNAP).

ARA-A was initially given in a dose of 10 mg/day intravenously for 10 days. DNAP fell immediately in all patients. In three patients activity returned on stopping treatment and HBsAg, HBeAg, and Dane particle positivity did not change. In the fourth patient DNAP remained absent after treatment and this was associated with falling levels of HBsAg, absent HBeAg and Dane particles.

Repeat courses of ARA-A in two patients showed that a higher dose of 20 mg kg⁻¹ day⁻¹ and more prolonged treatment for 21 days again produced a rapid fall in DNAP but this reappeared on stopping treatment.

ARA-A has activity against HBV in HBsAg + ve CLD but short courses may be insufficient to eradicate the virus. Further studies are under way to determine optimum treatment regimes.

Evidential value of the hospital record in clinical decision-making

W. I. CARD, W. SIRCUS, AND A. N. SMITH (Gastro-Intestinal Unit, Western General Hospital, Edinburgh; Diagnostic Methodology Research Unit, Southern General Hospital, Glasgow) In a formalised structure of medicine the activity of the doctor could be analysed as a sequence of decisions each based on the evidence he elicits¹. Part of this evidence may be in the medical record of a past illness. The problem is: what facts need to be recorded about an illness which would have evidential value should the patient be readmitted?

A retrospective study was undertaken of 53 readmissions to a gastrointestinal unit. Evidence about the present state of the patient and, if indicated, from the record of the past illness, was sought from a 'referee', by a physician and a surgeon. In a simulated exercise they used this information to arrive at the diagnosis and management. A numerical estimate was made of the evidential weight of each item requested, its degree of irrecoverability, and its benefit to the patient.

Each piece of evidence was given a score, and the total score derived from each source of evidence for all the patients compared. The sources of evidence in order of importance were operation findings, pathology, laboratory, radiology, and endoscopy. Other sources contributed little or none. It is concluded that, given the diagnosis at discharge and the details of any operation performed, the evidence worth recording could be specified; this evidence would be brief and could be numerically coded.

Reference


Faecal bile acid (BA) excretion in patients with cholelithiasis before and during chenodeoxycholic (CDCA) and ursodeoxycholic (UDCA) acid therapy

M. T. PODESTA, C. A. MCCLUFFIE, G. M. MURPHY, AND R. H. DOWLING (Gastroenterology Unit, Guy's Hospital and Medical School, London) During CDCA and UDCA therapy of gallstones, in increased amounts of potentially hepatotoxic lithocholate form, but do not accumulate appreciably, allegedly because hepatic sulphation prevents their intestinal reabsorption¹ but resultant changes in faecal excretion have never been studied. Furthermore, why some patients treated with CDCA get diarrhoea, while others, and UDCA-treated patients, do not, is unknown.

Therefore in 14 controls, five untreated gallstone patients, 12 taking CDCA (six with diarrhoea and six without) and seven taking UDCA, we measured total and individual faecal BAs before and after solvolysis² (which removes sulphates) and correlated findings with faecal wet weight.

Results showed that total faecal bile acid output (mg/day) was comparable in controls (60 ± SEM 106), untreated patients (845 ± 64), and in patients without diarrhoea taking CDCA (864 ± 186) or UDCA (650 ± 165), but was significantly increased in patients with diarrhoea (1333 ± 178; p < 0.005). Stool weight also correlated with total faecal BA excretion (r = 0.54; p < 0.001) and with excretion of non-sulphated cathartic (CDCA ± DCA) BAs (r = 0.56; p < 0.001). Contrary to expectation¹, lithocholate excretion (mg/day) was not increased during CDCA (86 ± 49) or UDCA (94 ± 34) when compared with untreated patients (192 ± 82).

We conclude that CDCA-induced diarrhoea occurs mainly with high faecal
BA excretion; lithocholate sulphate excretion is not increased during BA therapy.

References

COELIAC/LIVER AND BILIARY

Coeliac disease presenting as malabsorption from the tropics

R. M. MENDELSON, S. G. WRIGHT, AND A. M. TOMKINS (Hospital for Tropical Diseases, London, and Department of Human Nutrition, London School of Hygiene and Tropical Medicine) In a series of 274 patients fully investigated over a five year period for persisting symptoms of malabsorption after return from the tropics, 85 had giardiasis and 100 had tropical malabsorption (including 47 with tropical sprue). Thirteen cases had subtotal villous atrophy on initial jejunal biopsy. Six of these had persistent severe mucosal lesions despite elimination of giardia from three and treatment for tropical sprue in one.

Gluten withdrawal in these six patients resulted in improvement in symptoms and villous morphology. Reintroduction of gluten in three thus far has resulted in relapse.

Before tropical exposure these patients were asymptomatic and well-nourished. We suggest that acute gastrointestinal infection precipitated symptoms in these patients with coeliac disease.

We conclude that (1) a severe mucosal lesion and (2) the failure to improve after treatment for giardiasis or tropical sprue should suggest the diagnosis of coeliac disease.

Splen ic size and function in coeliac disease

P. J. ROBINSON, A. W. BULLEN, R. HALL, R. G. BROWN, AND M. S. LOSOWSKY (Departments of Radiology, Haematology, and Medicine, Leeds (St. James's) University Hospital, Leeds) There is increasing evidence that hyposplenism has adverse clinical consequences, some potentially avoidable. A substantial proportion of patients with coeliac disease have impaired splenic function as shown by measurement of heat-damaged red cell clearance, but this method is time-consuming, and complex. The technically simpler procedure of scintiscanning has shown small spleens in some immunologically abnormal coeliac patients, but correlation between splenic size and function has not been fully assessed.

Splenic scintiscans were performed after measurement of **\( \text{Tc} \) labelled heat-damaged red cell clearance in 28 coeliacs and six controls. **\( \text{Tc} \) sulphur colloid scans were performed in 24 coeliacs and 10 controls. Splenic volumes computed from colloid scans correlated well with those from red cell scans (\( r_s = 0.889, p < 0.001 \)). Correlation between splenic volume computed from red cell scans and heat-damaged red cell clearance in the coeliacs was good (\( r_s = -0.715, p < 0.001 \)). Eleven out of 28 coeliacs had both prolonged red cell clearance and computed splenic volume below the normal range; three patients were abnormal on one or other test.

Splenic function is impaired in about 50\% of patients with coeliac disease.

**\( \text{Tc} \) sulphur colloid scintiscanning provides a simple quantitative method of assessing splenic function which can be used in exploring the possibilities of avoidance of the adverse effects of hyposplenism.

References

Is prolactin trophic to the intestine in coeliac disease?

FIONA M. STEVENS, C. F. MCCARTHY, AND A. CRAIG (Department of Medicine, Regional Hospital, Galway, Ireland; Searle Diagnostic, High Wycombe, Buckinghamshire) Prolactin has been measured by radioimmunoassay in the blood of 13 untreated and 42 treated coeliac patients. Raised values were found in four of the five untreated male patients (558 ± 229 mU/l) (mean ± 1 SD) (normal range < 350 mU/l)). The levels in seven of the eight untreated female patients (325 ± 160 mU/l) (mean ± 1 SD) fell within the normal range (< 650 mU/l)).

Raised prolactin values (799 ± 1089 mU/l) (mean ± 1 SD) were found in 35 patients responding favourably to the gluten free diet. Significantly lower levels (\( p < 0.001 \)) were found in seven patients not responding to the diet (1314 ± 45-6 mU/l) (mean ± 1 SD). The finding of persistently raised prolactin values on serial sampling suggests that stress is not a contributing factor. No other known cause of hyperprolactinaemia could be defined.

In spite of the evidence in rats that perphenazine or pituitary transplant induced hyperprolactinaemia does not affect the growth of intestinal villi, the present results, together with the villous hyperplasia of lactation in rats, indicate that a possible enterotropic role for prolactin, or an associated hormone, needs further investigation.

Reference

Subcellular distribution of organelle-associated enzymes in untreated coeliac disease

R. W. LOBLEY, P. W. PEMBERTON, RITA WARWICK, G. I. SANDLE, AND R. HOLMES (University Department of Gastroenterology, The Royal Infirmary, Manchester) To investigate the subcellular distribution of organelle-associated enzymes in coeliac disease, jejunal biopsies from controls and patients with untreated coeliac disease were homogenised in isotonie mannitol, and four subcellular fractions isolated by differential centrifugation.

In coeliac homogenates, the specific activity of sucrase (brush-border enzyme) was 11\% of control (\( 2p < 0.002 \)); that of monooamine oxidase (mitochondria) was 22\% (\( 2p < 0.002 \)); non-specific esterase (endoplasmic reticulum) was 30\% (\( 2p < 0.002 \)) and \( \beta \)-N-acetylglucosaminidase, \( \beta \)-galactosidase and acid phosphatase (lysosomes) were 99\% (NS), 91\% (NS) and 147\% (\( 2p < 0.02 \)) respectively. Compared to controls, the proportion of sucrase present in the brush-border

The British Society of Gastroenterology
fraction of coeliac’s was significantly reduced and that in the microsomal and soluble fractions increased. β-N-Acetyl-
glucosaminidase, β-galactosidase, and acid phosphatase were each reduced in the brush-border and increased in the soluble fraction, but acid phosphatase was unique in showing increased microsomal and soluble specific activity.

Thus in untreated coeliac disease (1) the fragility of brush-borders and lysosomes is increased; (2) lysosomal enzyme activity may be generally unchanged, but (3) acid phosphatase is increased, suggesting either a different origin for this enzyme or a specific derangement; (4) mitochondrial and endoplasmic reticulum fractions may be impaired.

Serum lysozyme levels in malignant histiocytosis of the intestine

J. R. HODGES, P. ISAACSON, O. E. EADE, AND RALPH WRIGHT (Southampton University Hospitals, Southampton) A group of lymphomas associated with villous atrophy and malabsorption have recently been characterised as malignant histiocytosis of the intestine. Our finding of a markedly raised serum lysozyme level in two such cases suggested that this estimation may help in distinguishing malignant histiocytosis from uncomplicated adult coeliac disease.

Serum lysozyme levels were significantly raised in a group of eight patients with malignant histiocytosis of the intestine (P < 0.001); four were markedly raised. In contrast, there was no significant difference between groups of patients with uncomplicated adult coeliac disease and healthy controls. Three lymphoma patients’ sera had been stored for three years and in only one of these was the level raised. Comparison of lysozyme levels in control sera stored for three years or more with those obtained recently showed significant loss of lysozyme activity of long-term storage, so that the levels of stored sera from lymphoma patients may originally have been much higher.

The estimation of serum lysozyme is a simple test to perform and may be valuable in the diagnosis of malignant histiocytosis of the intestine and, in particular, in differentiating it from uncomplicated adult coeliac disease.

Ulcerative jejunitis: its relationship to malignant lymphoma

P. ISAACSON AND J. R. HODGES (Departments of Pathology and Medicine, University of Southampton Medical School, Southampton) Ulcerative jejunitis (non-granulomatous ileojejunitis) is a condition characterised by multiple ulcers of the small intestine which is frequently associated with long-standing malabsorption but which may be preceded by a very short history. The condition carries a high mortality caused by perforation of one or more ulcers. The histology of these ulcers is usually described as non-specific polymorphic chronic inflammation and jejunal villous atrophy with crypt hyperplasia has been a feature of all reported cases. The finding of small foci of malignant lymphoma in three cases presenting as ulcerative jejunitis, the development of small intestinal lymphoma six months after resection of three jejunal ulcers in another case, and the presence of multiple ‘benign’ ulcers in two cases presenting as primary small intestinal lymphoma, has led us to conclude that multiple small intestinal ulcers occurring in association with jejunal villous atrophy is a manifestation of intestinal lymphoma. The malignant lymphoma is of the type recently characterised as malignant histiocytosis of the intestine. Based on these conclusions, a series of investigations is suggested in patients with unexplained jejunal ulceration to rule out malignant lymphoma.

Effects of prostaglandin El (PGE1) on water and solute movements in the jejunum of patients with adult coeliac disease (ACD)

R. MODIGLIANI, P. COUZIGOU, E. RENE, M. HAUTEFEUILLE, P. BORIES AND J. J. BERNIER (Unité de Recherches sur la Physiopathologie de la Digestion U54, Hôpital Saint Lazare, Paris, France) In order to test in man the concept that intestinal fluid secretion originates from the crypts of Lieberkühn, we assessed the jejunal secretory effect of intraluminal PGE1 (0-9 μg kg-1 min-1) in active ACD (n = 11), treated ACD (n = 6) and normal subjects (n = 48), using the intestinal perfusion technique. A 130 mM Na-30 mM mannitol and a 130 mM Na-30 mM glucose solutions were perfused basally and during PGE1 administration. In active ACD (1) water and solutes were malabsorbed (or secreted)

Serum conjugated cholic acid in liver disease

M. VAN BLANKENSTEIN, J. W. O. VAN DEN BERG, M. FRENKEL AND F. J. W. TEN KATE (introduced by J. R. BENNET) (Department of Internal Medicine II and Department of Pathology I, Erasmus University, Rotterdam) The hypothesis that fasting and especially post-prandial serum bile acid levels are a sensitive test of liver function has been investigated by determining serum conjugated cholic acid (CCA) values fasting and one and two hours after a liquid test meal in over 250 patients undergoing liver biopsy.

The fasting and highest post-prandial (stimulated) CCA-values in various diagnostic categories were compared with values found in 23 normal healthy volunteers (controls).

No significant difference in fasting and stimulated CCA-values was found between controls and patients with: normal biopsies, minimal lesions and chronic persistent hepatitis.

In hepatitis with SGPT < 10 × normal, stimulated but not fasting values were significantly raised. In chronic active hepatitis, alcoholic steatosis with fibrosis, cirrhosis, primary biliary cirrhosis, acute hepatitis with SGPT 10-20 × normal, portacaval shunts and acute hepatitis with SGPT > 20 × normal, mean fasting and stimulated values were significantly higher than controls, with, however, overlap in
all but the last two categories.

Stimulated values improved discrimination only in acute hepatitis with SGPT < 10 × normal and alcoholic steatosis. These results indicate that (1) mean CCA-values are significantly raised in moderate to severe liver disease only; and (2) minimal improvement in sensitivity is obtained by post-prandial determinations.

Demonstration of a circulating antibody to halothane altered hepatocytes in patients with hepatitis

D. VERGANI, G. MIELI-VERGANI, A. ALBERTI, A. L. W. F. EDDLESTON, M. DAVIS and R. WILLIAMS (Liver Unit, King's College Hospital and Medical School, London) Because many of the clinical features of halothane hepatitis suggest an immune mediated pathogenesis, we have looked in patients with this condition for circulating antibodies directed against halothane altered hepatocyte membrane components.

Isolated hepatocytes were prepared from rabbits 12 hours after a 60 minute period of halothane anaesthesia, and incubated with sera from two patients with presumed halothane hepatitis. These had previously been adsorbed with normal hepatocytes to remove any antibodies reacting with normal cell surface constituents. Using indirect immunofluorescence, an antibody coating the surface of halothane pre-treated hepatocytes was visible as a distinct pattern of membrane fluorescence. This could be abolished by a second adsorption with halothane pre-treated hepatocytes.

To investigate the possible relationship between this antibody and cell-mediated cytotoxicity to hepatocytes, the two adsorbed sera were incubated in tissue culture with isolated liver cells obtained from halothane pre-treated rabbits. When lymphocytes from normal individuals were added to this system, strong cytotoxicity was induced, but only when using sera from patients with halothane hepatitis.

Thus patients with halothane hepatitis have a circulating antibody directed specifically against halothane altered hepatocyte membrane components. These can induce normal lymphocytes to become cytotoxic to liver cells obtained from halothane pre-treated rabbits.

Anti-LSP antibody in acute viral hepatitis

R. M. MELICONI, A. ALBERTI, D. JENSEN, I. G. MCFARLANE, A. L. W. F. EDDLESTON and ROGER WILLIAMS (Liver Unit, King's College Hospital and Medical School, London) Immune responses to a liver membrane lipoprotein (LSP) have been implicated in the pathogenesis of chronic active hepatitis. In this study we have used a sensitive radioimmunoassay to look for antibody to this antigen in serial serum specimens from 26 patients with acute viral hepatitis; this condition sometimes progresses to chronic liver disease. Of 21 patients with an uncomplicated course, 20 (95%) had detectable anti-LSP antibody in the first two weeks of the illness with titres of 1:40 to 1:3400. Antibody titres were similar in the 14 type B and the seven non-B cases. In three of the HBSAg positive group presenting very early in the course of the disease, highest anti-LSP values were found when first tested, before the peak in serum aminotransferases, when viral DNA polymerase levels were high, indicating active viral replication. Anti-LSP and DNA polymerase levels then fell in parallel. In all the patients with an uncomplicated course anti-LSP titres fell rapidly, but in five patients with a protracted clinical illness high levels persisted beyond three months. These results show that anti-LSP production in acute type B hepatitis is not simply secondary to liver damage but may be linked to viral replication.

Effect of penicillamine on immune complexes and immunoglobulins in primary biliary cirrhosis (PBC)

O. EPSTEIN, D. DE VILLIERS, S. JAIN, B. J. POTTER, H. C. THOMAS AND S. SHERLOCK (Department of Medicine, Royal Free Hospital, London) Twenty eight patients with PBC were randomly allocated either into a treatment group receiving 600-900 mg penicillamine daily, or a control group. Patients were followed for up to 24 months. Fifty per cent of patients had raised levels of circulating immune complexes. After 12 months' therapy, serum immune complexes (measured by 125I-C1q binding) had fallen significantly in treated patients compared to controls (p < 0.05) and this effect was sustained after 24 months (p < 0.01). Initially IgM concentrations were increased in the majority of patients, while IgA and IgG concentrations were normal. Treatment resulted in a fall in all three classes of immunoglobulins, with IgM concentrations being significantly different from controls after six, 12, and 24 months (p < 0.01). There was no evidence that penicillamine caused deggregation of immune complexes. Aspartate transaminase levels fell in response to treatment, while a sustained increase occurred in controls (p < 0.01 at six, 12, and 24 months), Bilirubin concentrations increased at a slower rate in patients receiving penicillamine, but the significant difference between groups at six months (p < 0.01) and 12 months (p < 0.05) was not apparent after 24 months. In addition to its copper chelating effect in PBC, penicillamine may favourably influence the course of the disease by its immunological action.

Comparative effects of short-term feeding of chenodeoxycholic and ursodeoxycholic acid on hepatic metabolism in man

N. CARULLI, F. ZIRONI, M. Ponz De Leon, A. PINETTI, AND P. FERRARI (Istituti di Clinica Medica, Clinica Chirurgica e Chimica organica Universita di Modena, 41100 Modena, Italia) Both chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA) administration reduce biliary cholesterol secretion and promote gallstones dissolution. It has been suggested that a possible mechanism could be the reduction of cholesterol synthesis by the liver. We decided to compare the effects of short term feeding of both CDCA and UDCA in equal dose (10-15 mg/kg/day) on bile lipid and biliary bile acid composition, cholesterol content of the liver and the two rate-limiting enzymes of cholesterol and bile acid synthesis, HMG-CoA-reductase (HMG-CoA-R) and 7a-hydroxylase (7a-OH).

Twenty-four gallstones patients were randomly divided in three groups; (A) eight untreated; (B) eight treated with CDCA and (C) eight treated with UDCA. The treatment was started seven to eight days before cholecystectomy. In groups B and C bile samples were obtained before and after the treatment. The liver samples (100-200 mg) obtained at the operation were used for biochemical assays and morphological examinations. The results are shown below by groups.

HMG-CoA-R 7a-OH pmol/mg prot.
Hepatic ultrastructure in Gilbert's syndrome: evidence for two populations

J. Dawson, D. L. Carr-Locke, I. C. Talbot, and F. D. Rosenthal (Departments of Medicine and Pathology, Leicester General Hospital, Leicester, and Department of Medicine, Royal Postgraduate Medical School, London) Gross hypertrophy of the hepatocyte smooth endoplasmic reticulum on electron microscopy has been suggested as a diagnostic feature of Gilbert's syndrome. Characteristic bilirubin responses after 48 hours on a 400 calorie diet or 180 minutes after intravenous injection of 50 mg nicotinic acid have also been reported. We studied hepatic ultrastructure in 24 patients and correlated the findings with response to caloric restriction and nicotinic acid. The smooth endoplasmic reticulum was hypertrophied in only 12 patients (EM positive) but did not differ from normal controls. The EM positive group showed a significantly greater mean percentage rise in bilirubin after caloric restriction (92.8 ± 16.8 SEM) compared with the NM negative group (46.1 ± 10.1, p < 0.05), who were similar to normal controls (39.5 ± 10.9). The mean percentage bilirubin response to nicotinic acid was higher but not significantly so in the EM positive (61.0 ± 17.8) compared with the EM negative group (32.5 ± 7.4), who were similar to normal subjects (43.5 ± 12.8). The two groups were otherwise similar in respect of mean bilirubin (33.7 ± 3.5 μmol/l; 40.2 ± 7.7 μmol/l), age, clinical presentation and mean red cell survival.

We suggest that smooth endoplasmic reticulum hypertrophy is not a constant feature of Gilbert's syndrome but is a characteristic of a distinct subpopulation.

References


Comparison of colonic motor function in diverticular disease and the irritable colon syndrome

J. Hyland, C. Darby, P. Hammond, and L. Taylor (Departments of Surgery and Bioengineering, Liverpool) It is often suggested that the irritable colon syndrome (ICS) is a pre-diverticular condition and it may be that patients with diverticular disease and predominant diarrhoea are really suffering from ICS.

In this study colonic motor function was compared in 20 patients with diverticular disease (seven with predominant diarrhoea), in 20 patients with ICS (seven with predominant diarrhoea) and in eight controls. Patients with diarrhoea were matched for symptom score, stool weight, and transit time. An intraluminal suction electrode was used to record sigmoid myoelectrical activity and the percentage of 2.4 c/m and 6.9 c/m activity was calculated using an automated frequency analyser.

No statistically significant difference in the incidence of these two frequency bands was found between patients with diverticular disease and normal controls. The ratio of the percentage incidence of each was 0.85 and 1.1. However, in ICS the mean incidence of the 2.4 c/m frequency was statistically significantly greater than 6.9 c/m (ratio 2.2).

Treatment with bran (12 g per day) resulted in a normalisation of stool weight and transit time in patients with diverticular disease and diarrhoea but not invariably so in ICS. Thus, on the basis of colonic motor function, there appears to be no evidence to link these two conditions.

Energetics of the colonic epithelial cells (colonoocytes) in man: the concept of energy deficiency diseases of the colonic mucosa

W. E. W. Roediger and S. C. Truelove (Nuffield Department of Clinical Surgery and Clinical Medicine, Radcliffe Infirmary, Oxford) Colonoocytes require energy for sodium pumping and for cell growth. We wished to establish the types of metabolic fuel utilised by normal colonoocytes of the ascending (AC) and descending colon (DC) in man.

Mucosae were obtained from colectomy specimens (seven AC, seven DC). Colonoocytes were prepared by incubating mucosal strips in calcium-free Krebs-Henseleit saline with 10 mM EDTA, 4 mg/ml hyaluronidase or 20 mM DL-dithiothreitol and 0.25% w/v bovine serum albumin.

Aerobic glycolysis was observed in both AC and DC. Glucose oxidation accounted for 85-4% of the oxygen consumption in the AC and 29-6% in the DC. In the presence of 10 mM β-butyrate these proportions decreased to 40-5% in the AC and 15-8% in the DC. The percentage oxygen consumption attributable to n-butyrate, when this was the only substrate, was 72-6% in the AC and 75-1% in the DC. In the presence of 10 mM glucose these proportions changed to 59-2% in the AC and 72-0% in the DC. We conclude that n-butyrate, under the conditions of study, is the predominant fuel of colonoocytes, particularly those of the DC.

In vivo, n-butyrate produced by bacteria is freely available to colonoocytes. In the light of the above findings and the work of others, there is the possibility that antibiotic diarrhoea is due to a mild temporary deficiency of butyric acid and that ulcerative colitis is due to a chronic persistent failure to utilise n-butyrate.

References

Cholinergic innervation of human small intestine

A. N. CHATTERJI (introduced by Professor L. A. TURNBERG) (Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) It has been suggested that control of ion transport by intestinal epithelial cells may be influenced by acetyl choline (ACh), released from nerve fibres near the mucosa.

To explore this hypothesis, the distribution of cholinergic nerve fibres in 15 specimens of human small intestinal mucosa was studied by light and electron microscopic (EM) cytochemical techniques.

Light microscopy revealed a dense network of cholinergic fibres extending throughout the intestinal wall. At the EM level, abundant nerve fibris were identified in the lamina propria of the villi and adjacent crypts. However, cholinergic fibres, recognised by specific reaction product localised to axon membranes, were shown not to be in contact with villous epithelial cell membranes, nor in close opposition to the basement membrane (BM). The minimum separation between BM and nerve fibres was at least 1 micron. Nerve fibres were in close apposition to crypt epithelium.

It is concluded that the intestinal wall has a rich cholinergic innervation, specially around the crypts, although the distance for ACh diffusion into villous epithelium through basement membrane is considerable.

These observations would suggest that if cholinergic fibres influence epithelial ion transport they do so via the crypt rather than villous epithelium.

References

Demonstration of opiate receptors in intestinal mucosal epithelium

J. S. MCKAY, P. C. HAWKER, B. D. LINAKER, AND L. A. TURNBERG (University Department of Medicine, Hope Hospital (University of Manchester School of Medicine), Salford) The demonstration of opiate receptors in brain and intestinal muscle raises the possibility that endogenous opiates (endorphins) play a physiological role in these tissues. Because of the known effects of opiates in diarrhoea therapy, we searched for evidence that such receptors exist in intestinal mucosa by which means opiates may influence intestinal transport.

Using an *in vitro* technique, segments of rabbit ileal mucosa, stripped of muscle layers, were clamped between Perspex half chambers and bathed in oxygenated bicarbonate/saline buffer. Morphine (2 × 10⁻³ M) caused a fall in potential difference (0.36 mV, p < 0.001) and short circuit current (8.2 μA/cm², p < 0.001) but resistance was unchanged (n = 20). Morphine increased net chloride absorption (from -0.19 to +1.98 μEq cm⁻² h⁻¹, p < 0.02, n = 10) due to a decrease in the serosa to mucosa unidirectional flux. Sodium transport was unaffected by the calculated residual ion flux, probably indicating that bicarbonate secretion was increased. Naloxone (10⁻⁶ M) enhanced rather than antagonised this response. Dextromoramide acted similarly but laevomoramide was inactive, suggesting that this was not a non-specific effect. Ileal secretory responses to prostaglandin E₂, theophylline or acetyl choline were not blocked by morphine.

These results indicate that opiates enhance ileal chloride absorption. The response to naloxone suggests the existence of a novel type of opiate receptor on the mucosa.

Reference

Migrating motor complex in man: its association with transjejunal potential difference

N. W. READ (Department of Physiology, University of Sheffield, Sheffield) We have previously described a temporal relationship between fluctuations in intraluminal pressure and transmural potential difference (PD) in the human small intestine and given evidence that the latter may represent electrogenic secretion of anions. We have now investigated the association of the PD with the recurrent phases of fasting motor activity known as quiescence, intermittent activity, and the migrating motor complex (MMC). Intraluminal pressure and transmural PD were recorded over seven hours from three jejunal sites (20 cm apart) in eight healthy fasted volunteers, using catheters perfused with saline. MMCS were observed in all subjects (duration = 10.8 ± 1.4 min; rate of propagation = 3.7-0.4 cm/min; period between complexes = 105 ± 12 min; mean ± SEM). The average PD during the MMC (−5.3 ± 0.5 mV) was significantly higher than the PD during intermittent activity (−2.7 ± 0.5 mV), which was significantly higher than that observed during quiescence (−1.3 ± 0.3 mV). Moreover, the migrating motor complex was accompanied by a single large migrating PD hump, while intermittent activity was associated with irregular PD fluctuations, some of which accompanied peristalsis and progressed at a much faster rate than the MMC (approximately 100 cm/min). These results suggest that different phases of intestinal motor activity may be associated with different rates of intestinal secretion.

Reference

Effects on pyloric reflux of antral and duodenal pacing in the cat

J. MUNK, M. HOARE, C. J. C. KIRK, AND A. G. JOHNSON (Professorial Department of Surgery, Charing Cross Hospital Medical School, London) Pyloric reflux probably depends far more on the relative contraction patterns either side of the pylorus than on the diameter of the pyloric ring itself.

Bipolar silver recording electrodes were permanently implanted in the antrum, pylorus, proximal, middle, and distal duodenum. In addition, stimulating electrodes were inserted in the antrum, proximal and distal duodenum, and any two of these could be stimulated at the same time. Synchronous radiology monitored the movement of 5 ml isotonic barium sulphate suspension introduced into the duodenum through an indwelling cannula. Recordings were started at least one week after operation while the animals were lightly sedated with Saffan.

Distal duodenal pacing consistently produced pyloric reflux. Synchronous proximal duodenal pacing reduced the
reflux but did not abolish it. Strong antral activity, produced spontaneously, by pacing or the administration of metoclopramide, did not completely prevent reflux but rapidly emptied the refluxed duodenal juice from the antrum so that it did not reach the fundus. Prolonged duodenal pacing produced vomiting in some animals.

It is suggested from these experiments that the cause of duodenogastric reflux should be sought in abnormal or independent duodenal activity rather than the diameter or response of the pylorus itself.

**Colonic inhibition of gastric secretion in man**

R. JIAN, J. HOSTEIN, C. AYMES, H. BESTERMAN, S. BLOOM, AND J. C. RAMBAUD (Research Unit on Pathophysiology of Digestion, Hôpital Saint Lazare, Paris, France) The colon has been shown to contain endocrine cells, whose role is unknown. We therefore studied in 12 healthy volunteers the influence of colonic perfusion of various solutes on gastric secretion and circulating levels of gastrointestinal hormones. Gastric secretion was stimulated by pentagastrin infusion at a constant rate (0-1 μg kg⁻¹ h⁻¹) and continuously aspirated through a Salem’s tube. Constant infusion of PEG 4000 allowed assessment of gastric juice recovery. Four hundred millilitres of each solute were perfused into the colon during 20 minutes after a two-hour basal period.

Hypertonic (823 mOsm kg⁻¹) glucose, mannitol, and saline solutions induced a prompt and sustained inhibition of gastric H⁺ and pepsin outputs: the mean percentages of H⁺ output inhibition were 74 (p < 0-01), 66 (p < 0-01), and 68 (p < 0-01) % respectively. Isotonic glucose and triglyceride had a much lower inhibitory effect.

Hypertonic glucose and mannitol colonic infusions had no effect on plasma levels of GIP, VIP, serotonin, somatostatin, and neurotensin. Both solutes increased circulating enteroglucagon; however, the effect of mannitol was much weaker than that of glucose.

These results suggest that gastric secretion can be inhibited by a presently unknown humoral substance of colonic origin.

**Single scan technique for estimating maximal acid output**

T. V. TAYLOR, S. HOLT, G. P. MCLoughlin, and R. C. HEADING (Departments of Clinical Surgery, Medical Physics and Therapeutics, Edinburgh Royal Infirmary) Gastric accumulation of ⁹⁹ᵐTc estimated by continuous aspiration of secretions has been shown accurately to correlate with acid secretion in the dog and man. Using a non-invasive method of estimating ⁹⁹ᵐTc uptake by the stomach, it has been shown that duodenal ulcer patients have a higher accumulation of isotope than those with gastric ulcer and gastric cancer. This non-invasive technique has now been correlated with conventional measurements of maximal acid output and the optimal timing for the scan has been investigated.

Thirty-six patients with mixed gastric-duodenal pathology have had their maximal acid output estimated conventionally and by ⁹⁹ᵐTc scanning in response to pentagastrin (6 μg/kg). Fifteen minutes after pentagastrin ⁹⁹ᵐTc (1 mCi) was given intravenously and scans were performed at 15, 30, and 45 minutes. The intragastric activity at 15 minutes, expressed as a percentage of the total injected dose of the isotope, correlated with that at 30 and 45 minutes (r 0-09). Of the patients studied four had pernicious anemia, five gastric cancer and 27 duodenal ulceration. The correlation coefficient between maximal acid output and intragastric activity was 0-88.

This non-invasive test of gastric function gives an accurate estimate of maximal acid output using only one scan taken 15 minutes after injection of ⁹⁹ᵐTc.

**References**


**Role of gastric acid secretion in the generation of human interdigestive motor activity**

W. D. W. REES, L. J. MILLER, J.-R. MALAGELADA, V. L. W. GO (Introduced by S. F. Phillips) (Gastroenterology Unit, Mayo Clinic, Rochester, Minnesota, USA) The release of motilin by gastric acid entering the duodenum has been suggested as a mechanism for generating interdigestive motor cycles. This study tested this hypothesis by examining fasting motor activity and plasma motilin during cimetidine-induced achlorhydria.

Fasting motor activity was recorded from the antrum, duodenum, and proximal jejunum of five healthy volunteers using intraluminal pressure transducers during nine hours on two days. Intravenous saline was given on one day and cimetidine (300 mg/4 h) on the other, in randomised sequence. During the last three hours of each day the duodenum was perfused with 0-1 N HCl using a 50 ml bolus and continuous infusion (5 ml/min). Intragastric pH and plasma motilin were measured at 15 minute intervals. Cimetidine produced achlorhydria (mean gastric pH: cimetidine = 7-5 ± 0-3; saline = 2-0 ± 0-4) but failed to alter interdigestive motor activity (mean cycle duration: cimetidine = 108 ± 16, saline = 90 ± 11 min; mean phase duration: cimetidine I = 64 ± 8, II = 39 ± 9, III = 5 ± 1 min; saline I = 54 ± 6, II = 30 ± 7, III = 5 ± 1 min). Cyclic variation in plasma motilin was observed on both days (range: cimetidine = 129-349, saline = 119-370 pg/ml). Intraduodenal acid inhibited cyclic motor activity in all subjects but produced a significant and sustained motilin release.

We conclude that (1) interdigestive motor cycles and cyclic release of motilin occur in achlorhydria; (2) intraduodenal acid stimulates release of motilin but inhibits interdigestive motor activity; (3) entry of gastric acid into the duodenum is not essential for generation of interdigestive cycles of motor activity.

**Is the chemical half life of cimetidine relevant to its duration of action?**

V. P. GERSKOWITCH, H. K. ADAM, E. J. DOUGLAS, AND C. L. HUGHES (Research Department, ICI Pharmaceuticals Division, Alderley Edge, Cheshire) The effect of cimetidine on stimulated acid secretion in relation to blood levels has been determined in Heidenhain and Pavlov pouch dogs.

Intravenous infusion of cimetidine at 0-7 and 1-0 mg kg⁻¹ h⁻¹ gave steady state plasma concentrations of between 800 to 1550 ng/ml after two hours. By subsequent challenge with histamine (30 and 90 μg kg⁻¹ h⁻¹ s.c.) or pentagastrin (0-5 μg kg⁻¹ h⁻¹ i.v.) this plasma concentration was found to correspond to 80-95% inhibition of acid secretion. Observing plasma levels and the rate of return of acid secretion to predetermined control values after discontinu-
ation of cimetidine infusion enabled both the biological and chemical half life to be calculated.

The effective concentration (EC_{50}) of cimetidine in these studies (~600 ng/ml) agrees with published values. The chemical half life was 72 ± 7 (mean ± SE) in contrast to the biological half life of 37 ± 7 minutes. The 2:1 ratio in half lives was observed in all our studies.

The unexpected difference between chemical and biological half life may be due to (1) biotransformation or (2) selective elimination from the site of action. The latter appears more probable in view of our findings of high concentrations of cimetidine in gastric juice.

This abbreviated biological half life may be of clinical relevance in that certain patients may have an unexpectedly shorter duration of biological effect.

**Effect of cimetidine on gastric acid secretory mechanisms**

**PHYLLIS A. MOONEY, JACQUELINE M. WALTERS, J. M. O’DONNELL, AND C. F. MCCARTHY (Department of Medicine, Regional Hospital, University College, Galway and Department of Pharmacology, University College, Galway)**

Little is known about the effect of cimetidine on biochemical mechanisms within gastric mucosal cells, which lead to gastric acid secretion and transport. The objectives of this project were to study the effects of cimetidine on levels of cyclic nucleotides and histamine-activated ATPase in gastric mucosa of patients with duodenal ulcer (DU).

Biopsies were taken for diagnostic purposes from the antrum and body of 12 patients, before and after one month of cimetidine treatment. Biopsies were also taken from patients with dyspepsia who had normal endoscopies. ATPase was assayed in biopsy homogenates and cyclic nucleotides were measured by radio-immunooassay.

Results showed that histamine-activated ATPase was present only in biopsies from the body of the stomach. This enzyme activity was higher (p < 0.02) in biopsies from patients with untreated DU, than in biopsies from patients who had normal endoscopies. There was no difference found in the histological characteristics of biopsies from these two groups of patients.

The levels of histamine-activated ATPase were reduced (p < 0.005) while cyclic AMP levels were increased (p < 0.001) after one month of cimetidine treatment. These results suggest that cimetidine may exact a marked influence at a cellular level on several biochemical mechanisms involved in gastric acid secretion transport.

**References**


**Gastric mucosal levels of peptigen I and II and their relationship to serum peptigen I and II**

L. J. LIBMAN AND I. M. SAMLOFF (Division of Gastroenterology, Harbor General Hospital, Torrance, California, USA)

The peptic cell mass for peptigen II (PG II) in pyloric and oxyntic gland mucosa, is greater than for peptigen I (PG I) present only in oxyntic mucosa.1,2 However, serum PG I levels are normally higher than serum PG II levels.3 In this study, PG I and PG II levels were determined by rocket immunoelctrophoresis in endoscopic gastric biopsies from 12 controls, six duodenal ulcer patients, and six with a gastric resection. In controls oxyntic mucosal PG I (µg/mg tissue protein), 55.9 ± 8.4 (mean ± SE) was significantly higher (p < 0.01) than oxyntic mucosal PG II, 21.7 ± 4.6. PG II in pyloric mucosa 87 ± 1.8, was significantly lower (p < 0.02) than in oxyntic mucosa. Serum PG I (ng/ml), 73.6 ± 11.8 was significantly higher (p < 0.01) than serum PG II, 32.6 ± 7.4. The mucosal PG I: PG II ratio 2.6:1, was similar to the serum PG I: PG II ratio 2:3:1. In duodenal ulcer patients PG I levels in oxyntic mucosa 87-8 ± 14-4, and serum 110-8 ± 29-3, were higher than controls. PG II levels in oxyntic mucosa 22-1 ± 5-0, and serum 46-2 ± 11-9, were similar to controls. In patients with a gastric resection both PG I and PG II levels in mucosa and serum were lower than in controls (mucosal PG I and PG II 28-6 ± 9-4 and 11-2 ± 2-5, respectively; serum PG I and PG II 25-5 ± 6.9 and 23-6 ± 5.9, respectively). Thus, as in serum, PG I is the predominant peptigen in mucosa. Mucosa peptigen levels are raised in duodenal ulcer patients and decreased in patients with gastric resection.

**Diffuse oesophageal spasm (D) and lower oesophageal sphincter spasm (C) are distinct entities**

W. C. WATSON, S. N. SULLIVAN, M. BELSHEIM, AND W. BERRY (G1 Unit, Victoria Hospital, University of Western Ontario, London, Ontario, Canada)

Thirty-three patients were allocated to diagnosis D (20) or C (13) on the basis of symptoms and manometric findings. Another five did not clearly fit either group. The manometric data were then analysed and compared. Reference points are S—lower oesophageal sphincter, F—5 cm proximal, T—10 cm proximal. In the basal or unstimulated state there was a significant difference between the mean pressures (mm Hg) at F in D 58, in C 43, p < 0.05) but not at T or S. After methacholine, 12.5 mg subcutaneously, significant changes occurred. In group D the mean pressure at T rose 55-4 (p < 0.001), at F 62-9 (p < 0.001) but at S only 7-9 (NS). In group C the mean pressure at T rose 14-7 (p < 0.05), at F 16-7 (p < 0.05), and at S 49-6 (p < 0.001). The differences between the degree of change at each point comparing the groups are highly significant—at T and F, p < 0.005, and at S, p < 0.001. Re-examination of the indeterminate group of five allowed a diagnosis of D in two. The remaining three were 'atypical', in that unusually high basal sphincter pressures (mean 113) fell after methacholine to mean 50. This paradoxical response may indicate a group of oesophageal motility disorders distinct from the entities of diffuse oesophageal spasm and lower oesophageal sphincter spasm.