HEPATITIS B VIRUS INFECTION AND OTHER VIROLOGICAL ASPECTS OF LIVER TRANSPLANTATION

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Experience with liver transplantation in the Cambridge-Kings College Hospital series since 1968 is now well documented.

Rejection and transmissible viral infections with which this communication is concerned are now more easily identified. Although initially considered a relative contra-indication by Starzl, we have transplanted four patients with serological evidence of hepatitis B virus infection, three with primary hepatoma, and one with chronic active hepatitis. All patients were given large doses of hepatitis B immune globulin, during the anhepatic phase of surgery and remained HBs Ag negative following the procedure. Often the bleeding tendencies of these patients necessitates transfusion of large volumes of blood and blood products with the attendant risks of transmissible viral infections.

Cytomegalovirus associated acute hepatitis has been observed in two patients, and in another, cirrhosis developed in the grafted liver and the aetiology was thought to be non-A non-B hepatitis viral infection. To date 92 patients have undergone this procedure, 28 have survived for over six months, and 18 for more than one year, and two have lived more than five years.

DISSEMINATED INTRAVASCULAR COAGULATION FOLLOWING PERITONEOVENOUS (LE VEEN) SHUNT

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The aim of this study was to determine the incidence, severity and clinical importance of disseminated intravascular coagulation (DIC) in the initial post-operative period following the insertion of a Le Veen shunt in patients with ascites. Ten shunts were performed in nine patients with ascites refractory to medical therapy. All had underlying portal hypertension and liver disease. Full coagulation studies were performed in all patients immediately pre-operatively and repeated at regular intervals in the initial post-operative period.

Two of the shunts failed to function in the immediate post-operative period as demonstrated by failure to mobilise ascitic fluid, increase urine volume and increase sodium excretion. Blockage was confirmed by radioisotope studies. Their clotting profiles were unchanged by surgery. In the remaining eight patients the shunts had a good initial flow and in all there was a deterioration in the coagulation profile consistent with DIC. In four of these patients this was associated with clinical evidence of impaired haemostasis which required surgical ligation of the shunt in two as an emergency measure. The other two patients died as a direct consequence of their bleeding.

Of the eight initially patent shunts, one blocked spontaneously and three others were surgically ligated in the early post-operative period. The clotting abnormalities in all these patients returned to pre-operative levels with the cessation of flow through the shunt. Four patients had continued shunt patency during their hospital stay and in all fibrin degradation products and fibrin monomers remained elevated. The conclusions reached are:

1. Adequate flow through peritoneovenous shunts causes laboratory evidence of DIC in all patients and this can be of major clinical importance.
2. DIC may account for the high spontaneous blockage rate.
3. Monitoring of the coagulation profile is a good index of continued shunt patency at least in the early post-operative period.

BREATH TESTS IN GASTROENTEROLOGY

G. METZ

Since the mid-1960s, increasing interest has been shown in the development of breath tests for the diagnosis of various gastrointestinal disorders.

Most tests are based on the measurement of exhaled 14CO₂, produced from the metabolic breakdown of a test substrate. The advantage of breath tests which involve the measurement of gases not normally exhaled in the breath, is that radio isotopic labelling is not required.

Earlier reports quantitated total respiratory output of labelled 14CO₂, but the simpler method of interval sampling has been shown to be adequate. Initial enthusiasm for a breath test in the diagnosis of fat malabsorption has been dampened by reports of “grey-zone” overlap. The test is likely to be useful as an outpatient screening test, but faecal fat data are still required in borderline cases. A 13CO₂ fat test may prove to be more accurate.

The 14C-glycine cholate test for bile salt degradation has been found to be adequately useful in aiding in the diagnosis of distal ileal disease, small intestinal bacterial overgrowth and cholangitis.

The 14CO₂ lactose test for disaccharidase deficiency was highly accurate but subsequently has been replaced by the hydrogen-lactose breath test which gives similar accuracy without the need to use isotopic labelling.

Breath tests of hepatic function are still under evaluation. A critical analysis of published data concentrating on 14-Carbon isotopic tests and H₂ breath tests will be presented.
PATIENT DISCOMFORT DURING COLONOSCOPY AND BARIUM ENEMA

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It is commonly stated that the patient discomfort is more severe during colonoscopy than during barium enema examination. To test this assumption, 50 patients undergoing routine colonoscopy completed a detailed questionnaire comparing the two procedures. Oral saline lavage preparation was rated as causing similar discomfort to standard barium enema preparation by 42% of patients. Thirty-four per cent preferred the lavage and 21% preferred the standard preparation. Discomfort during the actual examination was rated as greater during colonoscopy than during barium enema examination. To test this assumption, 70% preferred the lavage and 21% preferred the standard preparation. Discomfort during the actual examination was rated as greater during colonoscopy than during barium enema examination.

Comparison In 79 of the 84 cases cholecystogram and ultrasound agreed. Five cases had conflicting results: one false-positive for calculi with ultrasound; one false-ultrasound (bowel gas) with calcui on oral cholecystogram; three patients with normal cholecystograms in whom ultrasound showed calcui (2) or sludge (1).

Conclusion These two methods for gallstone evaluation seem equally reliable. It is suggested that a single dose oral cholecystogram be performed at the first visit, with immediate recourse to ultrasound if adequate visualisation is not achieved.

NON-A NON-B HEPATITIS

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Non-A non-B hepatitis is a recently identified but probably ancient and ubiquitous infection for which there may be more than one aetiological agent. The disease has been recognised as a complication of blood transfusion, the administration of factors VIII, IX and fibrinogen and is a major cause of sporadic hepatitis and is responsible for approximately 20% of all episodes of hepatitis leading to admission to this hospital. While non-A non-B hepatitis is usually a mild disease, persistent abnormalities of liver function are detected in up to 50% of patients of whom half show biopsy evidence of chronic liver disease.

Several groups have claimed to have detected specific viral particles in antigens in acute phase sera from patients with non-A non-B hepatitis, but to date none of these claims has been confirmed.

DIAGNOSIS OF GALLSTONES—COMPARISON OF ORAL CHOLECYSTOGRAPHY AND ULTRASOUND

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Ultrasound is now a well accepted alternative to oral cholecystography for the diagnosis of gallstones. This study has examined the relative accuracy of these two investigations in an attempt to develop a policy for their use in the radiology department of a busy teaching hospital. Eighty-four consecutive patients referred for oral cholecystogram were studied. A single dose of iopanoic acid was employed and if this resulted in only faint opacification or failure of opacification of the gall-bladder, the patient was given a repeat dose and returned the following day. All patients also had an ultrasound examination of the gall-bladder and biliary tree. The results were reported independently.

Oral Cholecystogram (84)—Sixty-two cases were reported as normal. Eleven patients had poor or non-visualisation of the gall-bladder; three refused surgery and in the remaining eight patients all had calculi found at surgery. In the final 21 patients, calculi were shown; in all eight who agreed to surgery, calculi were confirmed.

Ultrasound (84)—Adequate views were obtained in 83 cases; one failed due to excessive bowel gas. Fifty-eight cases were reported as normal. Twenty-four cases had calculi demonstrated; in 18 of 19 patients who had surgery, calculi were confirmed. The false-positive result was due to misinterpretation of sonic shadowing in the region of the gall-bladder neck. One case was reported to show "sludge" and at surgery, cholesterosis and chronic cholecystitis were found.

Comparison In 79 of the 84 cases cholecystogram and ultrasound agreed. Five cases had conflicting results: one false-positive for calculi with ultrasound; one failed ultrasound (bowel gas) with calcui on oral cholecystogram; three patients with normal cholecystograms in whom ultrasound showed calcui (2) or sludge (1).

Conclusion These two methods for gallstone evaluation seem equally reliable. It is suggested that a single dose oral cholecystogram be performed at the first visit, with immediate recourse to ultrasound if adequate visualisation is not achieved.

HYDATID DISEASE OF THE LIVER—ADVANCES IN SEROLOGICAL DIAGNOSIS

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The tests that have been most commonly employed for the diagnosis of hydatid disease in Australia include the intradermal test (ID or Casoni test), complement fixation test (CFT), indirect haemagglutination (IHA) test, latex agglutination (LA) test, indirect fluorescent antibody test (IFAT) and the immuno-electrophoresis test (IEP). More recently developed tests are the enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and countercurrent immunoelectrophoresis (CIE). This paper outlines the uses for immunological diagnosis of hydatid disease and the criteria for determining the test of choice in a particular circumstance. The usefulness of the tests in terms of the criteria set down will be discussed and examples will be given from results we have obtained in our laboratory during the last three years. At the present time, for pre-treatment diagnosis IHA and LA appear to be the best suited for screening purposes while IEP is the most specific diagnostic test. For post-operative follow-up IEP and the CFT are both useful.
HYDATID DISEASE OF THE LIVER

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The drug mebendazole has been used successfully against nematodes in man and animals and the intestinal phase of some cestodes in animals. Animal experimentation showed that mebendazole used intra-peritoneally caused regression of cysts in rats. Early work confirmed that due to the very low solubility of mebendazole absorption from the gastrointestinal tract could not be expected to produce effective systemic levels of the drug. However, following work with micronisation of the drug, increased absorption occurred in vivo and a systemic effect was expected; human evaluation was commenced.

The role of a chemotherapeutic drug in systemic disease is discussed and a review of cases presenting for treatment demonstrates that by the time the patient seeks help and the diagnosis is made surgical intervention must be the primary attack on the disease. However, great expectations can be held for a drug that will deal with the surgically inaccessible intestinal tract could not be expected to produce effective systemic levels of the drug. However, following work with micronisation of the drug, increased absorption occurred in vivo and a systemic effect was expected; human evaluation was commenced.

The relationship between hypogammaglobulinaemia and giardiasis has been clearly established. Associations with protein-calorie malnutrition and previous gastrectomy may exist but account for only a small number of cases in metropolitan centres. Recent studies suggest that the majority of adults in Australia have anti-giardia antibody in serum indicating previous exposure. Thus patients with prolonged symptoms apparently related to giardia may constitute a small group unable to spontaneously eliminate the parasite. Most of these patients have normal serum immunoglobulin levels but have a higher than expected frequency of the histocompatibility antigen HLA-B12.

Mebendazole, tinidazole and quinacrine eradicate giardia in the majority of patients although the optimal dose schedule remains unclear and two or three courses of treatment may be necessary. Demonstration of drug resistance must await in vitro tests of drug efficacy. Recurrence of giardiasis (as distinct from failure of eradication) appears to be rare in the absence of immune deficiency. The development of animal models of infection and techniques for in vitro culture of giardia trophozoites should enhance understanding of the biology and immunology of this most interesting parasite.

VIRAL GASTROENTERITIS—AN UPDATE!

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Two unrelated viruses are undoubted causes of acute gastroenteritis in man. These are Rotaviruses (70 nm) belonging to the family Reoviridae, and a group of unclassified parvovirus-like particles (27 nm) referred to as Norwalk agent and similar agents. Distribution of both groups of viruses is worldwide.

Rotavirus infection in childhood can be a serious threat to life, and is found in approximately 50% of children requiring admission to hospital with acute gastroenteritis in both temperate and tropical countries. Adequate early oral therapy reduces deaths in childhood in underdeveloped countries. Conflict over regimens of oral therapy to be administered by village mothers has slowed progress in this area. Vaccination with an oral attenuated strain of rotavirus is a possibility particularly after the recent success in adapting human type 2 rotavirus to cell culture.

Parvovirus-like agents (e.g. Norwalk agent, Hawaii agent, W-agent, Cockle agent) are usually associated with epidemics of nausea, vomiting and diarrhoea in older children and adults. Disease is self-limiting and may result from ingestion of contaminated food e.g. the recent epidemic in Australia associated with ingestion of oysters.

Other viruses proposed as aetiological agents of acute gastroenteritis include "astroviruses", caliciviruses, a variety of small viruses (28–32 nm) and coronaviruses. The latter may be implicated in chronic malabsorption and diarrhoea in some communities.

PSEUDOMEMBRANOUS COLITIS

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Pseudomembranous colitis is a rare complication of shock, septicaemia, renal or hepatic failure but now usually follows...
antibiotic administration, most commonly lincomycin, clindamycin, ampicillin or amoxycillin, whatever the route of administration. The disease will occur as late as three weeks after cessation of antibiotic and may persist for many weeks unrecognised. Clinically there is usually a non-bloody diarrhoea with varying toxemia and the diagnosis is based on the sigmoidoscopic recognition of the pseudomembrane. The latter however, may be missing in antibiotic-associated colitis and only non-specific reddening or ulceration of the rectum be present, resembling a non-specific colitis.

The disease is due to a *clostridium difficile* infection and the marked variability in incidence of the disease most probably reflects variation in the incidence of the organism in the external environment or in the gut lumen of the population. The infection can be diagnosed by detection of the toxin or by culture of *C. difficile* from the affected patient’s faeces.

While oral vancomycin appears to be an effective therapy, fatal relapse has been recorded and far from every case is severe enough to warrant the drug. Cholestyramine by binding the toxin may also help. The safety and efficacy of vancomycin remain subject to and there are unanswered questions such as whether isolation of the patient is desirable or whether there is ever a place for either the prophylactic use of vancomycin or its therapeutic use while continuing other antibiotic administration.

**THE SUBCELLULAR DISTRIBUTION OF LIVER COPPER IN NORMALS, PRIMARY BILIARY CIRRHOSIS AND WILSON’S DISEASE**

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Introduced by Dr. O. D. Harris

Excessive accumulation of copper is generally accepted to be the cause of liver damage in Wilson's disease (WD). Hepatic copper is also increased in primary biliary cirrhosis (PBC) but the pathogeneic significance is uncertain. Some animals store large amounts of copper in the liver without apparent harm (Goldfischer, 1970, Nature; 228, 172), appearing to store the excess copper in lysosomes. It has been widely suggested that lysosomal copper is non-toxic whereas extralysosomal copper is toxic. The subcellular distribution of liver copper in man has been previously studied but technical difficulties have severely limited interpretation of results.

Using "Percol" density-gradient centrifugation we developed a technique for measuring copper and have studied the subcellular localisation of copper in liver biopsies from two controls with normal liver copper levels and normal histology, three patients with PBC and five patients with Wilson's disease. Copper was measured by atomic absorption spectroscopy and organelles in the fractions collected were identified using specific marker enzyme assays.

There was no difference among the three patient groups in the proportion of copper found in the nuclear fraction (19%). In the post-nuclear supernatant copper localised to the cytosol and lysosomes in the ratio of 50:50 (controls) 64:36 (PBC) and 84:16 (WD). There was no evidence of either mitochondrial accumulation of copper, or increased lysosomal fragility in the copper-laden livers.

As liver copper increases in both PBC and Wilson's disease more is stored in the cytosol. Copper toxicity in Wilson's disease may be related to a failure to sequester the excess copper in lysosomes.

**EFFECT OF CIMETIDINE ON THE DISPOSITION OF THEOPHYLLINE**

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Recent evidence suggests cimetidine impairs warfarin, antipyrine and diazepam elimination. We have investigated the effect of cimetidine on the elimination of theophylline in two healthy controls, and three patients with chronic airways disease on maintenance theophylline. The control subjects received an intravenous infusion of theophylline 3 mg kg over 30 min and blood was collected for theophylline assay over the following 12 h. The next day antipyrine 18 mg kg was administered intravenously and blood collected over the following 48 h for antipyrine assay. Cimetidine 1 g day was then administered for five days and theophylline and antipyrine studies repeated. Theophylline and antipyrine were measured by high-performance liquid chromatography. In patients, oral theophylline 250 mg was administered 8th hourly and pre-dose samples collected and assayed daily for five days. On Day 5 interdose samples were collected hourly. Cimetidine 1 g day was started and collection and assay of daily pre-dose theophylline levels continued. After five days of cimetidine, interdose samples were again collected. In two patients and one control theophylline protein binding was measured by equilibrium dialysis. In the controls elimination half-life was prolonged for both theophylline (6.2 hr cf. 9.8 hr) and antipyrine (10.5 hr cf. 15.2 hr) and clearance decreased (theophylline 57.9 ml min cf. 38.4 ml min; antipyrine 49.3 ml min cf. 40.3 ml min) after cimetidine. In patients mean pre-cimetidine theophylline concentration was 5.0 ± 2.3 µg ml which increased to 7.6 ± 1.2 µg ml post-cimetidine. The interdose clearance in patients fell from 42.9 ± 5.6 ml min to 30.2 ± 3.4 ml min after cimetidine. Plasma protein binding did not change. These preliminary results suggest cimetidine impairs the elimination of theophylline.

**HEPATIC GLUTATHIONE AND HEPATIC DYSFUNCTION IN SURGICAL PATIENTS**

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Glutathione is an important component of hepatic cellular function and protects liver cells from exogenous and endogenous toxins. Hepatic clearance of exogenous dyes, a reliable test for hepatic function, is impaired when hepatic glutathione stores are depleted. Such depletion also results in an increase in the extent of hepatic necrosis when the liver is exposed to a potential hepatotoxin.

Many conditions, for example, fasting and low protein diet, are known to have a deleterious effect on the hepatic glutathione stores. However, no information is available concerning the effect on hepatic glutathione stores in patients with obstruction of the biliary tract and acute gastrointestinal haemorrhage. Hepatic dysfunction is present in the former, while post-operative jaundice is frequent in the latter.
We report here the hepatic glutathione levels in operative wedge liver biopsy specimens in three groups of patients: Group 1, "controls" (11 patients); Group 2, biliary obstruction with cholestasis (12 patients); Group 3, acute severe upper gastrointestinal haemorrhage (eight patients).

The control hepatic glutathione level was 4.20 ± 0.17 mmol g wet liver weight. The comparative values were 3.94 ± 0.20 mmol g wet liver weight for the obstruction group and 1.94 ± 0.18 mmol g wet liver weight for the haemorrhage group. In both surgical conditions studied, the hepatic glutathione stores were significantly depleted.

The deleterious effect on hepatic glutathione stores in biliary obstruction and acute blood loss may be accentuated by the often prolonged fasting and poor nutritional intake during the post-operative period. This may increase the hepato-toxicity of certain exogenous and endogenous substances, thereby contributing to the hepatic dysfunction in these two clinical situations.

### IDIOPATHIC HAEMOCHROMATOSIS: BIOCHEMICAL EXPRESSION OF THE CARRIER STATE

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Idiopathic haemochromatosis (IHC) is a genetic disorder determined by a locus on chromosome 6 tightly linked to the HLA A locus. The disease is clinically manifest in patients homozygous for the predisposing allele, consistent with a recessive mode of inheritance. Transmission of predisposing alleles in a pedigree can be traced by determination of HLA haplotypes, allowing identification of homozygotes (HH), heterozygotes (HO) and normals (OO).

In a study of 18 families with IHC, 35 subjects were identified as HH, 84 as HO, and 36 as OO. Serum iron concentration, total iron binding capacity (TIBC) and serum ferritin were measured in each subject. A liver biopsy was performed if any one of the above tests was abnormal. The three groups were compared with respect to each of the above investigations.

The relevant results are shown in the Table. There was a clear difference between HH subjects and the other two groups. Comparing HO and OO subjects, there was no difference in either mean serum iron or serum ferritin concentration. However, the mean TIBC was significantly lower in HO subjects, and the mean hepatic iron concentration was higher, compared to OO subjects.

| Serum iron | TIBC | Ferritin | Hepatic iron |
|------------|------|----------|--------------|
| (x ± SD)   | (x ± SD) | (x ± SD) | (x ± SD) |
| Homozygotes HH (15) | 41.4 ± 9.9 | 40.2 ± 7.0 | 610 ± 8 | 248 ± 5 (56.6) |
| Heterozygotes HO (84) | 21.6 ± 6.7 | 29.6 ± 7.5 | 59.2 | 358 ± 8 (21.2) |
| Normals OO (36) | 22.9 ± 6.4 | 65 ± 9.8 | 59.7 | 13.9 ± 2.1 |
| Level of significance | NS | P < 0.01 | NS | P < 0.05 |
| (HO vs OO) | NS | P > 0.02 | NS | P > 0.02 |

These data suggest that partial biochemical expression occurs in some heterozygotes, resulting in slightly increased hepatic iron stores. However, this was associated with neither clinical manifestations of iron overload, nor histological evidence of hepatic damage. The extent to which this slight increase in hepatic iron stores reflects total body iron stores remains to be determined.

### RECENT ADVANCES IN THE DIAGNOSIS AND MANAGEMENT OF SUGAR INTOLERANCE IN CHILDREN

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Presently available methods of diagnosing sugar intolerance in children are imprecise and often invasive, involving either small intestinal biopsy or multiple venepunctures.

Determination of lactase activity in small intestinal biopsies does not assess the total ability of the bowel mucosa to hydrolyse lactose. There is a poor correlation between jejunal lactase activity, jejunal histology, lactose tolerance testing and clinical lactose intolerance. The lactose tolerance test in infants and small children is unreliable giving both false positive and negative results in 20% of cases. Even the simple Clinitest method of measuring stool reducing substance is unreliable in the newborn period and will not be positive in all cases. It also relies on adequate collection of stool fluid and immediate testing, neither of which can be guaranteed in the ward situation.

The recently developed technique of breath hydrogen (H2) analysis circumvents many of the problems associated with more conventional tests of sugar intolerance. H2 is produced in the gastrointestinal tract by certain colonic bacteria fermenting unabsorbed carbohydrate and can be measured in expired air by gas chromatography. Approximately 5%, of children do not have H2 producing colonic bacteria. The value of this technique in the diagnosis, management and follow-up of children with post-enteritis sugar intolerance, sucrose intolerance, chronic diarrhoea and failure to thrive has been investigated. The test has been shown to be a rapid, specific and sensitive method for detecting carbohydrate malabsorption.

Children with acute diarrhoea produce satisfactory levels of H2 allowing discrimination between sugar tolerant and intolerant patients. The test is particularly helpful in the management of post-enteritis diarrhoea, chronic diarrhoea, sucrose intolerance, and is able to detect unsuspected bacterial colonisation of the small intestine which may present clinically with chronic diarrhoea.

### THE AGGREGATION OF HUMAN PLATELETS BY ASCITIC FLUID. A MECHANISM FOR THE DISSEMINATED INTRAVASCULAR COAGULATION (DIC) COMPLICATING LEVENE SHUNTS

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Disseminated intravascular coagulation (DIC) is a common problem in patients with Le Veen shunts. There is little doubt that this is caused by the infusion of ascitic fluid into the systemic circulation since ligation of the shunt is associated with cessation of DIC and patients who do not develop this complication usually have non-functioning shunts. The factor in the ascitic fluid responsible for the precipitation of DIC has not been previously recognised. This study is
concerned with the effects of ascitic fluid on human platelets and offers an explanation for the mechanism of DIC post Le Veen shunts. The addition of ascitic fluid concentrated five-fold to platelet rich plasma resulted in marked platelet aggregation which was inhibited by EDTA and adenosine. No aggregation was observed when aspirin treated platelets were used. The aggregating activity could be precipitated by band corresponding to type I collagen on SDS polyacrylamide gel electrophoresis. This dual activation would result in significant thrombin generation with the development of DIC.

Besides its ability to activate platelets, collagen can also activate the contact clotting factors namely factors XI and XII. This dual activation would result in significant thrombin generation with the development of DIC in vivo. Aspirin inhibits collagen induced platelet aggregation and would thus be expected to prevent or at least modify the complication of DIC post Le Veen shunts. This needs to be confirmed by a clinical study.

**IS VASOACTIVE INTESTINAL POLYPEPTIDE (VIP) AN INHIBITORY NEUROTRANSMITTER IN THE HUMAN STOMACH?**

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It has been suggested that VIP may be a neurotransmitter for non-adrenergic inhibitory nerves in the gut. Human gastric smooth muscle strips show nerve-mediated inhibition in response to electrical field stimulation (EFS). The inhibition is abolished by tetrodotoxin but is not reduced by atropine or adrenergic blocking agents. Strips of circular (6) and longitudinal (6) smooth muscle from human gastric antrum were suspended in a perfused tissue bath and stimulated with 2-10 sec trains of 1 msec, 50 V pulses at 10 Hz. All strips showed inhibitory responses to EFS in the presence of atropine. Serum containing antibody to VIP, when added to the perfusion fluid in concentrations of 1:1000 to 1:200 did not alter the responses to EFS. Similar results were obtained with strips of circular smooth muscle from possum lower oesophageal sphincter. The antibody had been generated by immunisation of a rabbit with natural porcine VIP conjugated to egg albumin. The serum binds 4 pmol/l of added VIP when used in a concentration of 1:100,000. It shows negligible cross-reaction with other gut hormones. Since the antibody should bind VIP released during nerve stimulation these results suggest that VIP is not a neurotransmitter for inhibitory nerves in the human stomach. (The VIP antibody was supplied by Dr. D. Byrnes.)

**OESOPHAGEAL DILATATION WITH EDER-PEUStOW DILATORS: FIVE YEARS’ EXPERIENCE**

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Between 1974 and 1980, 25 patients with benign peptic stricture underwent oesophageal dilatation on a total of 134 occasions. The average age was 65 and the male:female ratio was 2:1. Initial graded dilatations were carried out over a period of one to two weeks and repeated only if warranted by the patient's symptoms. No complications apart from chest discomfort and minor bleeding were experienced.

Eighteen patients had relief of symptoms after the initial dilatations and a further three had relief after a subsequent series of dilatations. Four patients had no relief of whom one was successfully dilated under general anaesthesia and the other three declined further treatment. Finally, in two patients, the guidewire could not be passed. The amount of dilatation varied but a 35F bougie was the minimum needed to ensure symptomatic improvement.

Of the 21 patients successfully dilated all but one required further dilatations 5-8 ± 4.8 months after the first. Some had a third dilatation after 7.9 ± 5.3 months. In five of the original responders the course was unsatisfactory: one is not fit for operation and the other four have required major surgery. Two patients have been lost to follow-up.

There are now 13 patients whose periods of follow-up vary from three months to four-and-a-half years, whose only treatment is regular dilatation with the Eder-PeuStow dilator. Four of these have been followed for more than two years. No carcinomas have developed.

We conclude that oesophageal dilatation by means of flexible Eder-PeuStow dilators is safe and effective and is the only surgical treatment required in many patients.

**THE INFLUENCE OF ORAL VITAMIN C SUPPLEMENTS ON EXPERIMENTAL COLO-RECTAL TUMOUR INDUCTION**

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Dietary vitamin C content is thought to influence the incidence of gastric carcinoma and vitamin C supplements have been claimed to reduce tumour development in multiple polyposis. Colo-rectal tumours were induced in inbred Fullendorf mice by weekly s.c. injections of dimethylhydrazine (DMH) at a dose of 15 mg/kg. Thirteen control mice were given oral distilled water, 11 mice were given oral vitamin C three times a week at a dose of 2 mg/week ("low dose vitamin C") and 10 mice were given the vitamin three times a week at 20 mg/week ("high dose vitamin C"). At 22-23 weeks all the animals were sacrificed. The colon and rectum from each animal was examined blindly and the number of macroscopic tumours counted. The control mice developed 23.8 ± 8.0 tumours/animal (mean ± SD), low dose vitamin C mice 30.9 ± 17.8 tumours/animal (P < 0.002) and high dose vitamin C mice 10.6 ± 6.0 (P < 0.0002). As in humans, tumours were found mainly in the distal colon.

Conclusion: Pharmacological doses of vitamin C protects against DMH induced colo-rectal tumours in mice and this may be of relevance in human colo-rectal carcinogenesis.

**TREATMENT OF THE IRRITABLE BOWEL SYNDROME BY PSYCHOTHERAPY**

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Following an earlier proposition that irritable bowel syndrome should be regarded as a psychophysiological
disorder. This study was undertaken to illustrate the influence of psychotherapy in the amelioration of IBS symptoms. Sixty consecutive patients seen in private practice between January 1976 and December 1977 were treated by psychotherapy. Organic disease was excluded by appropriate investigation. Three patients rejected the concept of an emotional basis for their symptoms and were excluded from the study; three patients were lost to follow-up.

A self-assessment questionnaire was sent to 54 subjects, two of whom failed to respond; the results of psychotherapy were assessed in the remaining 52 patients. Because of the chronic nature of their symptomatology the patients were used as their own controls. The 52 patients comprised 31 females aged 16-68 years (mean 39 years) and 21 males aged 14-60 years (mean 37 years). The duration of symptoms ranged from four months to 20 years (mean 5.5 years). Mean follow-up period since the last attendance was 20 months (range 8-33 months). A brief but active form of dynamic psychotherapy was adopted for all patients. Mean time spent in treatment was 2-2 hours and no patient received medication. Response to psychotherapy was graded from nil to 4+ (asymptomatic).

Results of the questionnaire indicated a substantial (3+ to 4+) improvement in 46%, of patients. Relief of individual abdominal symptoms to a similar degree was as follows: pain (42%, of patients); diarrhoea (69%); constipation (45%); and nausea (58%, of patients). The symptoms most resistant to treatment were pain and constipation where 24% and 35% of the subjects reported little or no change respectively.

The efficacy of a very brief but active form of psychotherapy in the treatment of IBS is supported. Results provide further evidence for a direct relationship between the psychological and somatic components of the disorder.

Reference
1. Holdop, G. (1971): Gut 12, 432.

DETECTION OF COLO-RECTAL TUMOURS BY HEMOCCULT: INFLUENCE OF PATTERNS OF BLEEDING AND SLIDE SENSITIVITY

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Colo-rectal cancer is often advanced when symptoms first develop. "Hemoccult II", a guaiac slide test for faecal occult blood, has been introduced for detection of asymptomatic colo-rectal cancers and adenomas. However, prediction of false-negative rates is difficult without information on patterns of bleeding from either asymptomatic or symptomatic lesions.

Gastrointestinal blood loss was measured by the radiochromium method for an average of 8-5 days in 49 patients. 31 with colo-rectal cancer (including 18 Dukes' A or B) and 18 with adenoma. Patients adhered to an occult blood diet and prepared Hemoccult slides in duplicate for development with and without rehydration.

Mean blood loss from eight right-sided cancers ranged from 2.5 to 25 ml/day, with most between 12 and 18 ml/day. All but one of 23 left-sided cancers had a mean loss below 6.5 ml/day. Expressed as concentration, significant blood loss (> 2 mg Hb/gm stool) occurred in each of 40 consecutive three-day periods from the right-sided cancers whereas bleeding was below this level during 42 of 137 cycles from left-sided cancers. Dukes' A and B cancers bled as much as more advanced lesions. Rehydration of Hemoccult slides increased their sensitivity at all levels of blood loss, doubling it at low levels. Hemoccult positivity was defined as one or more positive tests in any random consecutive three-day period. The false-negative rate for cancer was 30%, without rehydration and 8%, with rehydration. These rates were not altered if patients with overt bleeding were excluded. Most small adenomas did not bleed and were not detected by Hemoccult. In those > 2 cm. 75%, of cycles were Hemoccult positive.

These patterns of blood loss indicate that unrehydrated Hemoccult slides will miss at least 30%, of colo-rectal cancers. Detection of adenomas may be regarded as a bonus in screening programmes. Studies are in progress to evaluate the false-positive rates of rehydrated Hemoccult slides.

NUTRITION AND THE GASTROENTEROLOGIST

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Gastroenterologists have, inevitably, been more conscious of food and nutrition than most sub-specialists. It is therefore appropriate that they should express interest in new developments in human nutrition. Clinical nutrition embraces at least four areas: (1) Nutritional Assessment; (2) Nutritional Support; (3) Nutritionally-related Disorders; and (4) Nutrition Education.

Most of the nutritionally-related disorders in industrialised society are those of over-nutrition (obesity, atherosclerotic vascular disease, dental caries, certain neoplasms), but the gastroenterologist sees under-nutrition as far as "low dietary fibre intake", alcohol abuse, surgical complications, malabsorption and neoplastic disease are concerned and in special groups such as the elderly.

We have recently established a relationship between dietary fibre intake and bowel habits in pre-school children in the Latrobe Valley of Victoria. Alcohol abusers appear to be at risk from ascorbic acid and zinc as well as thiamin and folic acid deficiencies. Low serum albumins, found in institutionalised elderly, respond in part to zinc supplementation. Examples like these illustrate the application of new methodologies and horizons in clinical nutrition which may become relevant for gastroenterologists.

As the nutritional correlates of disorders of affluent society becomes clearer, a national nutritional policy can be formulated. Recommendations for dietary guidelines have now been made by an Australian Working Party, and include a reduction in energy intake, a reduction in alcohol intake, an increase in water intake, a reduction in fat intake and increases in whole grain cereal, fruit and vegetable consumption.

THE INFLUENCE OF SYSTEMIC ACID-BASE IMBALANCE ON THE DEVELOPMENT OF GASTRIC EROSIONS IN THE RESTRAINED RAT

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Recent studies of isolated sheets of amphibian gastric mucosa have indicated that HCO₃⁻ concentration bathing the mucosa...
determines, in part, the ability of the mucosa to tolerate acid. To extend these findings to a model which more closely approximates stress ulcers occurring in the critically ill patient, we have examined the influence of metabolic acidosis and alkalosis and respiratory acidosis on the development of gastric erosions in the cold restrained rat.

Male Hooded Wistar rats were restrained in tightly fitting perspex chambers at 6°C for 3 hrs. In seven rats metabolic acidosis was induced by infusion of NH₄Cl, 150 mM, at a rate of 1.5 ml/hr. This was via a carotid artery catheter. In 16 rats, metabolic alkalosis was induced by infusion of NaHCO₃, 150 mM, at a rate of 1.5 ml/hr. Respiratory acidosis was induced in six rats by maintaining the CO₂ concentration of the ambient gas at 5%. Arterial blood samples were taken and confirmed the expected changes in acid-base status for each group. At the completion of the period of restraint each rat was sacrificed and the stomach was examined. The severity of gastric erosions was measured on a scale of 0–4 (no damage to very severe damage).

In a control group of 17 rats with normal acid-base status the lesion score was 2.5 ± 0.25 (mean ± SEM). With metabolic acidosis the mean lesion score was 3.4 ± 0.26. This value is significantly higher than that noted in the control group (P < 0.05; Wilcoxon rank sum test). The rats subjected to metabolic alkalosis however showed a markedly lower lesion score of 0.6 ± 0.28 which was highly significantly different than control values. Respiratory acidosis was associated with a score of 2.0 ± 0.45 which was not significantly different from control values.

The results of this study indicate that the tendency to gastric erosions in the restrained rat is inversely related to the HCO₃⁻ concentration and appears to be independent of the pH or PCO₂.

**REFLUX ASSOCIATED LOWER OESOPHAGEAL SPHINCTER DYSFUNCTION IN PATIENTS WITH SYMPTOMATIC GASTRO-OESOPHAGEAL REFLUX**

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The pattern of basal lower oesophageal sphincter pressure (LOS) and its relationship to the occurrence of gastro-oesophageal reflux (GOR) was studied in 18 adult patients with symptomatic reflux. An intraluminal oesophageal pH electrode detected reflux episodes, and a seven lumen sleeve catheter assembly monitored continuously, pharyngeal, oesophageal body, lower oesophageal sphincter (LOS) and upper gastric pressures. With the patient supine, recordings were made with an eight-channel recorder for one hour prior to and for four hours after ingestion of a standard midday meal. Reflux episodes that caused oesophageal acidification ≤ pH 4 for at least 4 secs occurred at a mean frequency of 3·2/hour (SD ± 2·3) before the meal, and 3·4/hour (SD ± 3·8) after the meal. Reflux occurred only at times when LOS was equal to intragastric pressure. Abnormal basal sphincter tone was the predominant mechanism of reflux in only one-third of these patients. In these individuals sphincter pressure decayed gradually to zero after swallowing, or was persistently unrecordable (< 2 mm Hg). The majority of patients (67%) had recordable and usually normal basal LOS with a mean value of 18·4 mm Hg (range 5–53 mm Hg). Reflux occurred in these patients during 4–35 second episodes of abrupt total inhibition of LOS which were distinct from the LOS relaxation that is seen during a normal peristaltic sequence. Most commonly, these inappropriate LOS relaxations occurred without any identifiable precipitant, or directly after completion of normal oesophageal peristalsis. A variety of patterns of poorly integrated pharyngeal and oesophageal body motor events was also associated with inappropriate LOS relaxation.

We conclude that inappropriate inhibition of basal LOS tone is an important cause of supine GOR in patients with reflux disease. Many of these patients have normal basal sphincter pressure. The mechanism of this inhibition has not been elucidated by this study. In a minority of patients with symptomatic GOR, defective basal sphincter tone appears to be the major functional abnormality.

**EFFECT OF TOBACCO-SMOKE CONDENSATE ON MUCUS, PROTEIN AND DNA SYNTHESIS IN CULTURED ANTRAL MUCOSA**

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The mechanism of the peptic ulcerogenic effect of tobacco smoking is not known. Since tobacco smoke condensate (TSC) is swallowed during cigarette smoking, the possibility that TSC might adversely affect some mucosal function was explored. Synthesis of glycoprotein (mucus), protein and DNA by organ-cultured rat antral mucosa was assessed by measuring the incorporation of the respective precursors: ³H-fucose, ³H-leucine and ³H-thymidine. Triplicate plates were cultured for 5–20 hr in either control medium or medium containing TSC (10–1000 µg/ml). Explants were then homogenised and the radioactivity incorporated into tissue macromolecules measured. The results for synthesis during 20 hr of culture, expressed as d.p.m. of incorporated tracer/µg tissue protein (mean ± SE), were as follows:

|        | Glycoprotein | Protein | DNA    |
|--------|--------------|---------|--------|
| Control| 97±9×10⁻⁷    | 1460±66 | 117±8×22 |
| TSC (1000 µg/ml) | 417±5×2     | 459±105 | 42±9×5  |
| P-value| <0.01        | <0.01   | <0.05  |

At 5 hr, incorporation of labelled leucine, but not fucose or thymidine, was also significantly (P<0.001) inhibited by 1000 µg/ml TSC. At lower TSC concentrations, the differences from control values were not statistically significant at either 5 or 20 hr.

**Conclusions**: In cultured rat antrum, 1000 µg/ml TSC significantly impairs the three synthetic parameters measured. Such an inhibition of mucosal synthetic function, over a prolonged period of time, may be sufficient to account for the small excess of peptic ulcers observed in tobacco smokers.

**GASTRITIS AND DUODENITIS: AN ENDOSCOPIST’S VIEWPOINT**

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Advances in morphological understanding and histological classification have not improved clinical definition of gastritis and duodenitis. The use of these terms in frankly ulcerative lesions causes confusion and is probably the basis for the widely held view that gastritis and duodenitis of any sort may be the cause of haematemesis. Endoscopists lack acceptable working classifications for these conditions. Endoscopy
reports use descriptive terminology which is ill-defined and idiosyncratic. No general agreement exists as to the symptoms which are attributable to gastritis and duodenitis. The results of a survey of endoscopists’ views is presented. It is recommended that:

(a) Endoscopists indicate on reports if observed gastritis or duodenitis is likely to explain the patient’s symptoms.
(b) The terms “gastritis” and “duodenitis” be avoided in frankly ulcerative lesions.
(c) The Gastroenterology Society considers the formation of a body to examine a working clinical classification of the conditions.

GASTRITIS DUODENITIS—A PATHOLOGIST’S VIEWPOINT

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To the pathologist “gastritis” implies an inflammatory state of the stomach. Many have a known aetiology or occur as part of a disease which affects other parts of the gastrointestinal tract. Gastritis thus may be part of Crohn’s disease, eosinophilic gastritis, sarcoidosis, tuberculosis, syphilis, viral infections, etc. For the most part, however, the pathologist sees inflammatory changes in mucosal biopsy specimens when it is usually of entirely non-specific type and unassociated with a known aetiological agent. It is this form of gastritis which is seen in pernicious anaemia, peptic ulcer and occurs as an age related phenomenon. The distribution and features of this gastritis will be discussed and reasons advanced for believing that the lesion in pernicious anaemia is different from that occurring in the other two circumstances. Whether the development of ulcer and age related gastritis evolves through acute inflammatory episodes related to environmental or other factors will also be discussed. The importance of simple gastritis and concomitant intestinal metaplasia is considered in relation to gastric dysplasia and gastric cancer.

“Duodenitis” is viewed in a similar way, because inflammation of the duodenum may be part of a more widespread gastrointestinal disorder. In a proportion of individuals, however, inflammation of the duodenum may be present when the rest of the gut is normal. The controversy concerning the relationship of this lesion to dyspepsia and as a forerunner of duodenal ulcer is outlined. In this respect acute as opposed to chronic inflammation will be stressed.

Evidence about corticosteroids is conflicting but they probably do not produce this complication.

Although the drugs have differing mechanisms of action on the gastric mucosa, the endoscopic features are identical when damage does occur. The changes include patchy erythema, petechial haemorrhages, and single or multiple erosions, with involvement of any part of the stomach but particularly the antrum. The lesions heal rapidly, with restoration of the surface epithelium within hours after superficial injury, and within 3-7 days when erosions penetrate the mucosal progenitor zone.

The clinical significance of acute drug-induced lesions relates mainly to major upper gastrointestinal haemorrhage and to chronic blood loss during long-term drug therapy. There is no close correlation between the severity of endoscopic abnormalities and the presence of nausea or other gastrointestinal symptoms associated with drug ingestion.

The relationship between drug-induced mucosal damage and chronic atrophic gastritis is uncertain. Although prolonged treatment with aspirin can cause chronic gastric ulcer, the adjacent antral mucosa typically is normal, apart from acute or healing aspirin-induced erosions. As yet there is no convincing evidence to support prolonged treatment with anti-inflammatory drugs as a cause of chronic atrophic gastritis. Suggestions that chronic atrophic gastritis makes the gastric mucosa more susceptible to drug-induced damage deserve further investigation, as do suggestions of a relationship between anti-inflammatory drugs and acute duodenal injury.

GASTRITIS DUODENITIS. APPROACH TO THERAPY

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Chronic atrophic gastritis requires no treatment: regular surveillance for malignancy is not justifiable. Minor endoscopic and histopathological changes are over-interpreted by inexperienced investigators, leading to incorrect management. Gross diffuse, inflammatory changes or erosive changes are obvious. Pyloro-duodenitis is part of the spectrum of duodenal ulceration. Antral gastritis is difficult to heal. It is likely that gross gastritis/duodenitis produces dyspepsic symptoms and it causes acute and chronic gastrointestinal bleeding. It may lead to chronic ulceration. Predisposing courses include—aspirin, aspirin and alcohol, severe illness (ITU setting), partial gastrectomy and possibly other analgesics, other drugs and stress. Removal of these may effect a cure. Prophylactic therapy is justifiable in an ITU setting. Specific therapy includes—Cimetidine; Tri-potassium di-citrato bismuthate: Antacids in high dose; Carbexoxolone. Cimetidine is probably the most convenient and free from side effects. There is no evidence that any treatment causes permanent cure. The place of prostaglandins and antidepressants has not been defined. Large, prospective studies are necessary.

TEN YEARS AFTER PARIETAL CELL VAGOTOMY

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Parietal Cell Vagotomy (PCV) has become accepted by many surgeons throughout the world as the definitive operation for...
duodenal ulcer. Early results indicate that the procedure is associated with less sequelae than any other operation for duodenal ulcer. Diarrhoea and dumping has virtually been eliminated. However, reported early recurrence rates have varied widely. Five year recurrence rates have been reported by Jensen and Andrup, 9%; Goligher et al. 4-3%; and Jordan 11-4%. It is apparent that technical considerations are of prime importance in obtaining a low recurrence rate. Good results are obtained for all forms of gastric surgery in centres where the operation is performed frequently by competent surgeons.

Ninety-one patients were followed up completely, nine died of unrelated causes during follow up and 12 could not be followed for five years. There was no mortality in the whole group. Of the 70 patients with duodenal ulcer whose follow up was complete, 4 developed a recurrent ulcer, a recurrence rate of 5.7%. The clinical status of these patients assessed by Visick’s criteria revealed that 88% were either Visick I or II.

Ten patients had PCV for gastric ulceration. There were no recurrences in this group.

Eleven patients had PCV for pre-pyloric ulceration. In nine patients the ulcer recurred—a recurrent ulcer rate of 82%.

It is concluded that Parietal Cell Vagotomy is a safe and effective operation for duodenal ulceration but should not be undertaken for pre-pyloric ulceration.

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NEW APPROACHES TO VITAMIN B₁₂ MALABSORPTION

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The mechanism of vitamin B₁₂ (cobalamin) absorption provides a superb example of how knowledge of a series of physiological events contributes to the understanding of cobalamin malabsorption. Frank megaloblastic anaemia is an uncommon manifestation but testing with radio-labelled cyanocobalamin in the presence of added gastric intrinsic factor (GIF) helps in the recognition of the potential of cobalamin deficiency. This test provides an indirect means of recognising gastric lesions, including failure of secretion of GIF and the secretion of biologically inert GIF. Disturbances of intestinal microecology which lead to competition between bacterial receptors and GIF for cobalamin during the intestinal transit phase, and mucosal lesions of the ileum involving loss of GIF receptors through disease processes. Pancreatic insufficiency may also lead to impaired Cbl absorption. Recent work indicates that there is impaired digestion of the gastric R protein—cobalamin complexes in this state. Transfer of cobalamin to GIF normally occurs in the upper small intestine following destruction of the R protein by pancreatic proteases. These complexes are formed in the stomach in preference to GIF—cobalamin because of the higher affinity of the R protein for cobalamin. Although consideration of cobalamin malabsorption centres on how GIF-Cbl is delivered to the ideal epithelial surface, a disturbance of mucosal uptake of cobalamin after GIF—cobalamin is bound to its receptor may also contribute to malabsorption (Imerslund-Grasbeck syndrome). Preliminary evidence that the intestine is one of the sites of synthesis of the serum transport protein, transcobalamin II is relevant to the finding of cobalamin malabsorption when there is a congenital deficiency of this protein.

A RE-LOOK AT RECTAL PROLAPSE

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Complete rectal prolapse is an uncommon but distressing affliction, which probably occurs as the result of an intussusception of the upper rectum through the anal canal. This and other views about the aetiology will be described in detail.

Patients with complete rectal prolapse have a deep pelvic peritoneal pouch, diastasis of the levator ani, loss of the anterior angulation of the rectum and patulous anal sphincters. They almost invariably are incontinent of faeces, and this usually persists even after successful surgical repair of the prolapse.

The multiplicity of operations described for the treatment of complete rectal prolapse are testimony to the difficulty of surgical treatment. However, methods designed to fix the rectum to the sacrum are usually successful in treating the prolapse, but further procedures may be necessary when faecal incontinence remains a problem.

AN APPROACH TO THE INVESTIGATION OF PERSISTENT DIARRHOEA

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An approach to the investigation of persistent diarrhoea is based on experience with 100 consecutive patients. Weight loss remains the most important symptom and usually indicates an organic cause for the diarrhoea. The pattern of other symptoms was of little diagnostic importance. Sigmoidoscopy should be part of the routine physical examination and is likely to be of diagnostic value in 20% of subjects, with diagnoses including inflammatory bowel disease, rectal tumours, melanosis coli, solitary rectal ulcer and pseudomembranous colitis. The next step could be an empirical therapeutic course of either tinidazole or metronidazole; a significant group of subjects in whom giardia is not found will respond dramatically. Should small bowel biopsy be done before using tinidazole, then examination of the duodenal juice might disclose giardia trophozoites; histological examination and disaccharidase assay may show evidence of Coeliac disease and other mucosal lesions, or isolated disaccharidase deficiencies such as sucrose iso-maltase deficiency. The justification for barium studies needs to be carefully evaluated. It is evident that inflammatory bowel disease in the form of Crohn’s colitis or terminal ileum involvement must still be considered and barium enema might be the best way to proceed. There was little yield from a small bowel series. Full blood count is simple and inexpensive, although its diagnostic value may be small. Information from electrolytes, urea, creatinine and liver function tests was of no value even in presence of severe diarrhoea. The use of other sophisticated techniques such as colonoscopy, 3-day faecal fat estimation, pancreatic function tests, thyroid function studies, 24 h urinary 5HIAA, d-xylene absorption, immunoglobulins and serum carotene need to be justified on an individual basis.
HEPATIC VEIN THROMBOSIS

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Over the past nine years we have recognised six patients with this disease, four occurring in the last two years. Their ages ranged from 44-66 years. Four were female. Mortality was high, four died. In the two living recurring and refractory ascites has been a major problem. The main presenting feature in all but one was increasing abdominal girth over a period of one week to three months with a more rapid recent increase in three (the remaining one patient had coincidental malignant disease). Three had obvious lower limb oedema. Abdominal pain in five, lumbar back pain in two occurred at some stage during the course of the illness. Hepatomegaly was present in all patients. Polycythemia was found in half; a long history of oral contraceptive intake in one, a past history of recurrent deep venous thrombosis in one, an underlying breast carcinoma and cytotoxic treatment in one and HB,Ag Positive status in one. None of the patients had peripheral stigmata of chronic liver disease on presentation. Liver function tests were not helpful with AST varying from 36-2475U/L, alkaline phosphatase from normal to 8 times, bilirubin was always elevated from 25-123 mmol/l and plasma albumin was initially normal in four. Liver scans revealed poor tracer uptake in all patients with increased splenic and marrow uptake, but in only two was the typical caudate lobe distribution noted. Liver biopsy and venography were diagnostic each in four patients (although respectively in one). A variety of treatments including anticoagulants, peritoneovenous shunts for the control of ascites, and one portasacval shunt were used with only very limited success. All patients were diagnosed relatively late in the illness. Diagnostic laparotomy (performed in two) resulted in post-operative complications and death. Although diagnosis is difficult liver biopsy and hepatic venography +/- hepatic wedge pressure are the most likely investigations to make the diagnosis. Medical treatment alone is unsatisfactory. Awareness of the condition with earlier diagnosis and a more carefully planned medical and surgical approach may make a difference to prognosis.

ANGIODYSPLASIA CAUSING GASTROINTESTINAL BLEEDING IN EIGHT PATIENTS

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We report an experience of 8 patients with acquired and congenital vascular lesions (angiodysplasia) which adds to the description of this uncommon cause of gastrointestinal bleeding. Three patients had melena over a five to ten year period. One presented acutely with melena, two with haematemeses and two with rectal bleeding. The majority had multiple endoscopic examinations before the diagnosis. Lesions were found by upper endoscopy in six, colonoscopy in three and angiography in four. Telangiectases of skin or mucous membranes were found in three and one had multiple haemangiomas. Further details are shown in the table.

THE PRACTICE OF OESOPHAGEAL MANOMETRY, AND ITS PLACE IN PATIENT MANAGEMENT

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Primary investigation of suspected oesophageal disease with history, barium swallow and endoscopy is sufficient to establish a diagnosis in the majority of patients. Some patients however, have atypical or non specific symptoms due to motility abnormalities or oesophageal mucosal hypersensitivity. In these patients such abnormalities are detected unreliably by endoscopy or radiology, and in patients who have had oesophageal surgery these methods of investigation can be confusing or inconclusive. Carefully performed oesophageal manometry, acid infusion testing and intra oesophageal pH monitoring may, in these instances, establish a diagnosis and will usually aid management.

On the grounds of robustness and versatility, the external transducer perfused catheter system is most suitable for routine clinical manometry and research studies. Accurate measurements of oesophageal body and sphincter pressures will be obtained only if a specialized low compliance constant perfusion pump is used. Absolute values of oesophageal peristalsis are of diagnostic significance in patients with intermittent dysphagia or non cardiac chest pain. The large and brief pressure waves generated by the pharynx can only be measured accurately with miniature intraluminal transducers, but the clinical value of such measurements is not established. Intraluminal pH recording is a simple technique which can be used as a sensitive audit for the efficacy of antireflux surgery. The method also aids the evaluation of patients with atypical chest pain, and is a valuable research tool.

Possession of a high fidelity manometry system, and the ability to intubate the oesophagus should not be confused with the capacity for accurate performance and interpretation of oesophageal manometric studies. The pitfalls and technical details of oesophageal manometry are
such that measurements of diagnostic and scientific value will only be achieved if manometric studies are supervised and interpreted by individuals with a well developed special interest in the field.

HEPATOMA IN "LUPOID" CHRONIC ACTIVE HEPATITIS

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Although hepatocellular carcinoma is a recognised complication of cirrhosis it has not previously been described in patients with "lupoid" chronic active hepatitis.

Over the past five years we have seen 49 patients with primary liver cell carcinoma. (PLCC). 37 having cirrhotic livers. Four of these patients (mean age at death—57) had had known, well-documented "lupoid" hepatitis and had been followed for between five and 21 years, all receiving corticosteroid therapy. In all cases the initial liver biopsy showed the classical changes of chronic active hepatitis. Laboratory data in all revealed elevated transaminases and hypergammaglobulinaemia. In 3/4 patients smooth muscle antibody was positive in high titre. LE cells and anti-nuclear factors were present in 2/4. HBsAg as measured by radioimmunoassay was negative in 4/4 and HBcAb was negative in the two patients in whom it was measured.

Other "auto-immune" features in these patients included ulcerative colitis, polymyositis and erythema marginatum.

In all patients signs of liver cell failure heralded the development of PLCC although two patients had undergone portasystemic shunt surgery, in both four years prior to their demise. Alpha-foetoprotein as measured by R.I.A. was positive in 2/4. The clinical suspicion of PLCC was confirmed at autopsy in all cases.

The development of PLCC in these four cirrhotic patients with lupoid hepatitis probably reflects the increased life span afforded by corticosteroid therapy.

IMPAIRMENT OF AN HEPATIC PROTECTIVE MECHANISM IN MAN BY FOOD INGESTION

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The exposure of mammalian tissues to substances such as drugs and toxins which are absorbed from the gut depends on the extent of their initial ("first pass") extraction by the liver and their subsequent rate of removal from the circulation. Systemic exposure has been considered independent of hepatic blood flow and thus should be unaffected by physiological and pharmacological influences on liver circulation. This study has tested this hypothesis by examining the effect of food on the first pass clearance of oral propranolol.

Following the oral administration of propranolol to 7 normal volunteers the peripheral plasma concentrations of the drug have been measured at regular time intervals over 24 h. Propranolol was given either on an empty stomach or with a protein/lipid or carbohydrate rich meal. Under fasting conditions propranolol concentrations rose slowly to a peak between two and five h after dosing whereas ingestion of either test meal produced an earlier and increased peak concentration with up to a two fold increase in the systemic bioavailability of the drug.

The observed increased bioavailability could not be explained by food induced changes in absorption as recovery of a tracer oral dose of 14C labelled propranolol in the urine was not changed by food ingestion. Similarly systemic clearance of propranolol following intravenous dosing was unaltered by food. By exclusion these results indicate that the increased bioavailability of oral propranolol when given with food is due to a decrease in the first pass clearance of the drug by the liver.

These findings indicate that food intake and other factors which modify liver blood flow will have a profound effect on a patients systemic exposure to drugs, environmental toxins, nutrients and gut hormones and be of major clinical import.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF PANCREATIC POLYPEPTIDE (PP) IN MAN

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PP a 36 amino acid peptide discovered as an impurity of insulin preparation is localised in a distinct cell type in the islet and exocrine cells of the pancreas. Circulating levels of PP can be measured by a sensitive and specific radioimmunoassay. The physiologic role of PP is uncertain but it is probably an inhibitor of pancreatic and biliary secretion. Factors causing PP release are cholinergic, gastric and hormonal. Cholemic stimulation by insulin hypoglycaemia or modified sham feeding results in a rapid increase in PP levels which is inhibited by truncal vagotomy or prior anticholinergic blockade.

Gastrointestinal hormone(s) may also play a part as an impure extract of porcine intestine (Boots secretin) stimulates PP release. Which hormones may produce this effect is unknown as only pharmacologic doses of gastrin and cholecystokinin stimulate PP release and pure secretin does not.

Basal PP levels are high in elderly patients, those with renal failure, diabetes mellitus and more than half the patients with endocrine neoplasms of the pancreas. Basal and stimulated PP levels in duodenal ulcer patients are no different from controls but gastric ulcer patients have a significantly lower response. Chronic pancreatitis has a markedly reduced PP response to either a protein meal or Boots secretin whereas PP secretion in cancer of the pancreas is usually normal. The secretin stimulated PP response may become a useful test for the diagnosis of chronic pancreatitis.
ISOFERRITINS OF RAT LIVER HEPATOCYTES AND KUPFFER CELLS

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The aim of this study was to determine: (i) the contribution of the major cell types in the liver to the observed isoferritin profile of normal rat liver; (ii) the effects of liver regeneration and iron stimulation on their hepatic isoferritins. We examined the isoferritin (IF) composition of whole rat liver, perfused rat liver, isolated hepatocytes and of sinusoidal lining cells (Kf cells) and also of rat spleen and serum.

Isolated hepatocytes and Kf cells were obtained after perfusion with collagenase or pronase four days after partial hepatectomy. Ferritin concentrations were determined by RIA and the IF profiles were obtained by isoelectric focusing (IEF) and radiolabelling with specific antibody.

The IF profiles obtained from both the cytosol homogenates of rat whole liver and from isolated hepatocytes contained two major IF of pI 5.4 and 5.55. The IF pattern from isolated Kf cells also contained two major IF, one in common with hepatocytes (pI 5.55). The additional major IF of Kf cells was more basic than either major IF of hepatocytes (pI 5.6 approx.) and appeared to correspond to the most basic IF of rat serum (apoferitin) and whole liver.

Iron stimulation in vivo resulted in a decrease in the most basic IF demonstrable in Kf cells. This is consistent with the hypothesis that it corresponds to apoferritin. The IF profiles from regenerating liver five days after partial hepatectomy were identical to those of the resected liver prior to hepatectomy.

It is concluded that the IF profile of rat liver closely resembles that of hepatocytes. However, when the concentrations of hepatocyte and Kf cell ferritin are equal, the Kf cell ferritin shows a prominent more basic IF (pI 5.6). The apparent disappearance of this IF after iron stimulation is consistent with its being apoferritin.