Hepatoblastoma and APC gene mutation in familial adenomatous polyposis

Editor,—The recent article by Giardiello et al (Gut 1996; 39: 867–9) reported eight patients with hepatoblastoma collected from the Johns Hopkins Polypsis Registry. As the authors acknowledge, hepatoblastoma is very rare in patients with familial adenomatous polyposis (FAP). Only 33 cases (24 men, nine women) have been reported in the literature since the first description in 1982.1 In particular, the exact site of the APC gene mutation has been detected in only a minority of these patients.

Here, we report an additional patient with FAP associated hepatoblastoma, who was discovered during intensive screening of a consecutive series of FAP kindreds.2 The patient, a young girl, underwent liver resection for hepatoblastoma when two years old. She survived hepatic resection and is still alive and in good health. She is now 10 years old and has not developed overt colonic polyposis but has congenital hypertrophy of the retinal pigment epithelium (CHRPE). The patient belongs to an extended kindred (23 patients in four generations). There were seven affected patients in the last two generations. Five of them have already undergone colectomy for colonic polyps.1 Interestingly, three patients, all women, also had asymptomatic papillary thyroid carcinoma. Early detection of thyroid tumours was facilitated by the study protocol, which included systematic screening of the thyroid gland by ultrasonography. Two of the three resected thyroid specimens also showed aberrant expression of Ret/PTC, a chimeric gene that is restricted to the papillary histotype (Ret/PTC1 isoform).3 All affected patients of the present kindred have CHRPE, none have desmoid tumours, and all have a 5 base pair deletion ACAA (position 3183–3187) in exon 15 of the APC gene (codon 1061).4

Interestingly, this same mutation has also been reported in Giardiello et al’s series. This supports the view that patients with hepatoblastoma have APC mutations which tend to cluster in a particular genomic area, restricted to codons 141 to 1387. In our kindred there was one patient with hepatoblastoma and three with thyroid carcinoma.5 All of them also had CHRPE, but not desmoid tumours. These observations suggest that hepatoblastoma and thyroid carcinoma frequently co-segregate with CHRPE, but less frequently with desmoid tumours, which are particularly prevalent in patients with APC mutations beyond codon 1404.5

Intensive screening of FAP kindreds for all known extracolonic manifestations facilitates early detection and improves prognosis. Systematic ultrasound examination of the abdomen should be performed in young siblings of patients with FAP who have a liver lesion on physical examination. Further characterisation of the spectrum of APC mutations in FAP families with hepatoblastoma as well as characterisation of APC gene function in the liver will be the goal of future research.

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1 Kingston JE, Draper GI, Mann JR. Hepatoblastoma and polyposis coli. Lancet 1982; i: 457.

Depression, alcohol abuse and orocecal transit time

Editor,—We read with great interest the paper by Gorard et al (Gut 1996; 39: 551–5) on intestinal transit in patients with anxiety and depression. The authors used the lactulose hydrogen breath test to evaluate 21 consecutive outpatients attending a general psychiatry clinic who fulfilled DSM III R criteria for major depression or generalised anxiety disorders, or both. They reported a significantly prolonged orocecal transit time (OCTT) in depressed patients compared with anxious patients, and a significant correlation between whole gut transit time and the score of the psychometric tests used to assess depression, showing evidence for an association between severity of depression and colon inertia. The authors conclude that depressed patients tend to be constipated and that mood has an effect on intestinal motor function, although mechanisms by which mood can alter colonic motility remain unknown.

Recently, we found a significantly prolonged OCTT in patients with chronic alcoholism without severe liver disease compared with social drinkers and teetotal subjects.1 Thirty one alcoholic patients without diseases which could affect OCTT were enrolled in the study on the basis of DSM III R criteria. Mean alcohol consumption was 191.1 g/d (range 90–360) and the mean duration of addiction was 15.9 years (range 1–36). Thirty one healthy, social drinkers and 24 teetotal subjects matched the alcoholic controls were studied as controls. OCTT was assessed using the hydrogen breath test after administration of 10 g lactulose. The test was performed in the morning after a 12 hour fast. The concentration of expired H2, evaluated in parts per million (ppm) was measured before and at 10 minute intervals for four hours after administration of lactulose. An increase in the concentration of H2 > 10 ppm in at least three measurements of H2 during the baseline values was considered indicative of the arrival of the lactulose in the caecum. In one alcoholic, four social drinkers and two teetotal subjects no increase in hydrogen excretion of at least 10 ppm within 300 minutes after lactulose ingestion. These subjects were excluded from statistical analysis as the OCTT could not be evaluated. Three alcoholic patients had small intestinal bacterial overgrowth (19%) indicated by a rapid rise in breath hydrogen concentration during the first 45 minutes after ingestion of lactulose, and were excluded from statistical analysis. The OCTT in alcoholic patients (mean (SD) 156.3 (29.7) minutes, range 90–200) was significantly delayed compared with social drinkers (94.1 (11.3) minutes, range 70–120) and healthy teetotal subjects (85.5 (15.6) minutes, range 60–120) (fig 1). In alcoholic subjects there was no significant correlation between the OCTT and daily alcohol intake or years of alcohol addiction respectively. Our findings thus support the hypothesis that the toxic effect of ethanol on the smooth muscle contractile proteins of the small intestine and on vagal functions may be a causal factor of the dyspeptic symptoms in alcoholic patients. Depression and alcohol abuse both co-exist with a co-occurrence that varies from 16% to 68%;2 the co-morbidity between alcohol disorders and major depression has frequently been reported in alcoholic and psychiatric patient samples.3 The relation between depression and alcohol abuse has been difficult to define. Some authors have suggested that depressed mood is largely associated with the episode of drinking and may be due to the effect of chronic alcohol intoxication,4 whereas others have shown a consistent and significant association between depression and alcohol disorders providing persuasive evidence that major depression is a critical component of alcohol abuse and dependence.5

In the study by Gorard et al it is not reported whether alcohol abuse was investigated and considered as an exclusion criterion. If alcoholic patients were not excluded, this factor could be partly responsible for the prolonged OCTT in their depressed patients. Conversely, if the alcohol disorders were considered as exclusion criteria and only depressed patients were evaluated, Gorard et

11979; 41: 417–420

LETTERS TO
THE EDITOR
Alcoholics Social drinkers Teetotallers

![Figure 1: Orocaecal transit time in alcoholic patients, social drinkers and teetotal subjects.]


Reply

Editor,—We appreciate the interest that Addolorato et al have shown in our paper. We can verify that in our study none of the subjects drank alcohol excessively nor had a history of alcoholism. Therefore, the longer transit times in our depressed subjects cannot be attributed to increased alcohol use.

In the study by Addolorato et al showing prolonged OCTT in patients with chronic alcoholism, it is therefore possible that associated depression in their patients may have contributed to this result. These authors also postulate a possible toxic effect of ethanol on intestinal smooth muscle as the explanation for their findings, but other neurohumoral factors may be important. For example, alcoholic patients have high cortisol concentrations, as to a lesser extent do depressed patients, and corticotrophin releasing hormone is known to have inhibitory effects on upper gastrointestinal motor function. Furthermore, if their alcoholic patients were withdrawing from alcohol while participating in the study, then the stress of withdrawal with increased adrenergic tone could have contributed to prolonged OCTT.

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Chronic diarrhoea in AIDS

Editor,—We read with interest the article by Blanshard et al (*Gut* 1996; 39: 824–32) where a cohort of adult AIDS patients with chronic diarrhoea was investigated for potential stool pathogens. An extensive array of diagnostic tools was used, including microbiological examination of stools, duodenal aspirates, and microscopic examination of biopsy specimens from the duodenum, jejunum, and rectum. However, despite investigation for at least 20 bacterial, viral, and parasitic pathogens it seems a remarkable omission that no pathogenic *Escherichia coli* groups were sought.

Although routine microbiology laboratories now rarely seek stool *E coli*, other than enterohaemorrhagic *E coli* of serogroup O157, these organisms are readily isolated on MacConkey agar, and categories may be further differentiated using DNA probes or in vitro cell culture assays, or both, in the absence of serotyping facilities. Although one pilot study has found no evidence of a role for enteropathogenic *E coli* in diarrhoea in HIV infected patients, several others report such an association. Case reports have suggested that enteropathogenic *E coli* (EPEC) and enterogregarative *E coli* (EAEc) are possible causes of chronic diarrhoea in adult patients with AIDS and several groups have shown a highly significant association between HEP-2 cell-adherent *E coli* (including EPEC and EAEc) and chronic diarrhoea in adults with AIDS in Zambia and the USA.

In the latter two studies, as with Blanshard et al’s study, light and electron microscopic techniques were used to examine intestinal biopsy samples. In the preliminary study 17% of patients with AIDS had bacteria adherent to their intestinal mucosa in patterns indicative of several pathogenic *E coli* groups. The other study reported 52 patients with chronic diarrhoea and mucosally adherent bacteria associated with attaching-effacing lesions (characteristic of EPEC) or loosely associated with the mucosa (EAEc).

Although Blanshard et al were able to identify a potential pathogen in 83% of cases, the available literature suggests that pathogenic *E coli* could have accounted for a considerable percentage of those cases where no pathogen was found.

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Faecal elastase 1

Editor,—I read with interest a recent study by Löser et al (Gut 1996; 39: 580–6). This detailed and well designed study compares a new tubeless test of pancreatic function, faecal pancreatic elastase 1 (FPE1) assay, against the secretin test which is the accepted gold standard pancreatic function test. It had very good specificity and sensitivity for pancreatic insufficiency, confirmed by the secretin test and the presence of steatorrhea. The FPE1 assay in mild chronic pancreatitis, an abnormal function but no steatorrhea, had a much lower sensitivity of 63%. These results are not entirely different from our pilot study.1 The majority (nine of 14) of our chronic pancreatitis subjects were diagnosed by the secretin test and not anatomical/ radiographic criteria only. The other five subjects without a secretin test had chronic pancreatitis based on ERP, pancreatic calcifications and post pancreatic surgery. We did not have mild, moderate and severe categories. We chose to separate our patients with chronic pancreatitis into two groups, severe and moderate, based on an abnormal secretin test and the presence or absence of steatorrhea or malabsorption. We found that in those with chronic pancreatitis and no evidence of malabsorption (our moderate group) the FPE1 was normal in four of seven subjects and no values were in the range 100–200 μg/g of stool, the proposed concentration of FPE1 for moderate chronic pancreatitis. In our disease control group (steatorrhea from non-pancreatic aetiologies), four of seven subjects had abnormal FPE1 concentrations. This group was chosen as a key clinical decision point to decide whether or not steatorrhea results from pancreatic insufficiency. In the study by Löser et al., false positive results were also detected in the control group (gastrointestinal diseases of non-pancreatic origin). We wonder whether these subjects had steatorrhea?

Keywords: faecal elastase 1

The characteristics of pancreatic elastase 1, as well as the simplicity of using the FPE1 assay (ScheBo Tech), do support the clinical usefulness of this assay. Indeed, Löser et al.’s larger and well designed study shows that the test works well overall, but in the group most difficult to diagnose, it may be less sensitive. This group of patients with chronic pancreatitis present primarily with pain but without steatorrhea. They typically have normal pancreatic ducts on ERP, and are best diagnosed using the secretin test. We believe the secretin test is easy to use and is not significantly more invasive than a nasogastric tube. It is devoid of any real complications4 and correlates very well with the true gold standard, histology.1

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Reply

Editor,—The clinical relevance of a pancreatic function test is strongly related to its sensitivity and specificity in mild and moderate cases of exocrine pancreatic insufficiency, as severe cases with progressive steatorrhea are rarely a challenge in clinical practice. In our study all 14 patients with moderate exocrine insufficiency, defined as decreased ecbolic and hydrokinetic function in the secretin-caerulein test, but no steatorrhea, had significantly decreased faecal elastase 1 concentrations, giving 100% sensitivity in moderate cases. In patients with a partial decrease in ecbolic pancreatic function but no disturbance of hydrokinetic function and no steatorrhea, the sensitivity was 63%. Though this is a limited sensitivity for mild cases, it is by far the highest sensitivity reported to date for an indirect pancreatic function test. These data are actually confirmed by the results of further studies (see references 13–16, 26, 28).

We agree with Drs Amann and Toskes that the secretin test is not as difficult to use as thought by many clinicians, but there is no doubt that the FPE1 assay is more practical and easier to use. The secretin test is invasive, time consuming, uncomfortable for the patient, is not an international standard (this test procedure is uncommon in Europe), and is more expensive than the FPE1 assay. Despite certain limitations in very mild cases of exocrine pancreatic insufficiency, measurement of the faecal elastase 1 concentration is actually the most sensitive and most specific indirect pancreatic function test available.

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BOOK REVIEWS


This book is the second edition of a monograph in the Differential Diagnosis in Conventional Radiology series by Burgener and Kormano aimed at radiologists, physicians and surgeons interested in gastrointestinal radiology. There are chapters on the abnormal gaseous pattern including: dilatation and motility disorders, narrowing, and filling defects. There is also a chapter on ulcers, diverticula and fistulae, and one on biliary tract abnormalities.

There is lot of interesting material in this book that should prove helpful to those who wish to expand their knowledge of basic gastrointestinal radiology. In general, the book is well illustrated but there are exceptions, particularly in the chapter on ulcers, diverticula and fistulae. I would like to have seen an example of the typical appearances of an oesophageal web shown on lateral and anteroposterior projections.

There are, however, a number of shortcomings, particularly lack of attention to detail when describing or discussing some of the more uncommon disorders. In some cases the views expressed are out of date and I was left with the impression that neither of the authors have extensive experience in gastrointestinal radiology. On the first page it is suggested that the upright view of the abdomen is routinely used to show free intraperitoneal air, whereas the upright chest radiograph is now widely used for this purpose. The upright chest radiograph provides the best chance of showing small amounts of free intraperitoneal air because the horizontal x ray beam is tangential to the dome of the diaphragm. The current practice in a number of leading paediatric centres of using air instead of barium to reduce intussusception in infants is not mentioned, although hydrostatic reduction is discussed. When discussing neonatal necrotising enterocolitis, it is stated that gas in the portal vein indicates a probable fatal outcome. The presence of extensive pneumotosis intestinalis and portal venous gas indicates severe disease but does not necessarily predict an irreversible course. Gastrocolic fistulae resulting from benign ulceration are occasionally shown during a barium meal examination and I am reluctant to accept the views expressed that at the present time gastrocolic fistulae are mostly complications of malignancy, best shown by barium enema. There is a statement that entero-enteric fistulae are rare in ulcerative colitis (0.5%). Ulcerative colitis does not involve the small intestine and I am not aware that entero-enteric fistulae ever occur in this disorder.

These criticisms only relate to some sections and overall this book contains a wealth of information that is concisely presented. It is ideal for those who wish to find out about the many diverse disorders that can be diagnosed using conventional radiological techniques.

DANIEL J NOLAN


The Royal College of Radiologists is very keen that x-ray departments should be called Departments of Clinical Radiology in order to emphasise the strong links between clinical specialties and imaging. This book epitomises that philosophy. It is basically a radiological book written by a radiologist and a gastroenterologist, but contains hefty and valuable slices of comprehensive clinical material which should make it attractive to radiologists, gastroenterologists and surgeons with an interest in biliary and pancreatic disease. Its high quality radiological images, some of which are virtually unique, provide a useful atlas and it is sufficiently well referenced to
allow the reader who wishes to delve further to be successful. Its 14 chapters start with technical aspects of imaging and endoscopy, although it does not set out to be a significant practical guide to ERCP techniques. Chapters on normal anatomy, developmental anomalies, benign and malignant disease of the biliary system and the pancreas follow, and the book finishes with a series of useful tables of differential diagnosis and pattern analysis. All in all, this is an individual book which adopts a unique approach to its subject and at the price is well worth having.

D MARTIN


Considering the major advances in gastrointestinal therapeutics in recent years, it is timely that this book dedicated to gastrointestinal pharmacology and therapeutics should be published. Gastrointestinal Pharmacology and Therapeutics consists of 59 chapters divided into 15 sections on all aspects of gastrointestinal pharmacology. In fact, there is considerable emphasis on gastrointestinal pathophysiology so the book could easily be called Gastrointestinal Pathophysiology, Pharmacology and Therapeutics. It is written almost exclusively (apart from a token European), by American based gastroenterologists and pharmacologists and thus has quite an American feel to it.

The opening chapter discusses the fundamentals of gastrointestinal pharmacology. In other general pharmacology text books the section mainly dealing with pharmacodynamics and pharmacokinetics is generally avoided by students in the hope that they won’t get asked about this in examinations! However, in this book, the chapter is well illustrated and deals with the subject without being too stodgy. The book then goes on to go through the gastrointestinal tract starting with upper GI tract diseases leading with a convenient division up treatment into complications of oesophageal reflux, gastric and duodenal ulcers and drug-induced ulcerogenesis. Information given here for the most part is also acceptable this side of the water. There are, however, some inconsistencies. For example, in the chapter on drug induced ulcerogenesis it is recognised that “it is unknown whether an synergism exists between H pylori and NSAIDs to increase ulcer diathesis”, it then goes on to recommend eradication of H pylori for all patients on NSAIDs.

There is an excellent chapter on the pharmacology of small bowel infections which contains a lot of information on both viral and bacterial gastroenteritis and has a useful table on current antibiotic treatments for these conditions. There is also a useful up-to-date section on AIDS and the gut which deals with the oesophagus, stomach and colon in separate chapters.

The section on inflammatory bowel disease conveniently divides up treatment into commonly used agents in inflammatory bowel disease and drugs for which fairly minimal data are available or are still in the experimental phase. It then goes on to discuss the medical management of Crohn’s disease and ulcerative colitis in separate chapters. Both acute and chronic liver disease are then dealt with, with considerable emphasis on the pathophysiology of these conditions. Other chapters deal with acute and chronic pancreatitis, the pharmacology of bowel ischaemia and the use of drugs in pregnancy and old age. The concluding chapters are on the drug development process including an informative chapter on FDA regulations. It even contains a chapter on the role of the pharmaceutical industry in drug development along with some advice for would-be researchers on setting up clinical trials in gastroenterology and therapeutics.

This book is primarily aimed at practising clinicians dealing with day-to-day management of gastroenterological problems but who may not have access to libraries or resources for more extensive literature researching. In the forefront of this book it is stated that the problem of information overload is solved by this book. However, a major criticism of the book would be that there are too many chapters, many devoted to pathophysiology of various conditions which are covered comprehensively in many other general text books. For example, in the section on sphincter of Oddi pharmacology there is a whole chapter in the physiology of the sphincter of Oddi with one short paragraph on therapy. Despite these reservations, this is a general, comprehensive text book on gastrointestinal pharmacology and therapeutics and overall it is a worthy addition. It also is bound in a handsome dark green cover and priced at $183.00 it is not particularly expensive for what is given here for the most part is also acceptable this side of the water.

WILLIAM A STACK
CHRISTOPHER J HAWKEY

NOTES

SIR FRANCIS AVERY JONES BSG RESEARCH AWARD 1998

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1998 Award. Applications (TWENTY COPIES) should be made to the Honorary Secretary, BSG, 3 St Andrews Place, London NW1 4LB, by 1 December 1997.

FLAVIVIRIDAE SYMPOSIUM

The Flaviviridae Symposium will be held at the Palais des Congrès, Lyon, France, on 9 October 1997. Further information from: Dr F Zeytin, ICN Pharmaceuticals Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, USA. Fax: 001 714 668 3141; email: f.zeytin@icnpharm.com.

V INTERNATIONAL CONFERENCE: CURRENT TRENDS IN CHRONICALLY EVOLVING VIRAL HEPATITIS

The V International Conference: Current Trends in Chronically Evolving Viral Hepatitis will be held at the Palais des Congrès, Lyon, France, on 10 and 11 October 1997. Further information from Société Package, 53 rue Vauban, F 69006 Lyon, Cedex 02, France. Tel: +33 (0) 478 24 18 06; Fax: +33 (0) 472 74 18 33. Abstract deadline: 23 July 1997.

COURSE IN POSTGRADUATE GASTROENTEROLOGY

A Course in Postgraduate Gastroenterology will be held in Oxford, UK, on 4–7 January 1998. This course has been designed for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include:

- Liver disease
- Colonic neoplasia
- Acute pancreatitis
- Osteoporosis, arthritis and GI disease
- Food allergy and intolerance.

Course fee £200 ($330). Board and accommodation are available at Wadham College at extra cost. Six bursaries will be available for applicants training in gastroenterology or in research posts at British hospitals. Further information from: Dr DP Jewell, Gastroenterology Unit, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.

CORRECTION

Errors occurred in the shading of the columns of figure 3 in the paper by Boulant et al (Gut 1997; 40: 575–81). The correct figure is reproduced below.
Hepatoblastoma and APC gene mutation in familial adenomatous polyposis

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Gut 1997 41: 417-420
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