

LETTERS TO THE EDITOR

Timing of transfusion, anti-HBc, and hepatitis C virus related hepatocellular carcinoma

EDITOR,—Dr Marusawa and colleagues (*Gut* 1999;45:284-288), commenting on their findings of a high prevalence of antibodies to hepatitis B virus (HBV) core antigen (anti-HBc) in Japanese patients with hepatitis C virus (HCV) chronic liver disease, suggest that HBV infection has a role in the development of hepatocellular carcinoma (HCC) in patients with chronic HCV infection. I would like to raise a methodological point that may influence the interpretation of their findings.

HBV and HCV infections share common mechanisms of transmission and are highly correlated. Therefore, it is not surprising that the prevalence of anti-HBc was much higher in individuals with chronic HCV infection than in the anti-HCV negative controls. But why would patients with HCV associated HCC have a higher prevalence of anti-HBc than individuals with HCV chronic hepatitis and liver cirrhosis? Stratified analyses suggested this finding is not related to age or history of past transfusion, or to other risk factors that might have confounded this association. An alternative explanation to that provided by Marusawa *et al* is that the differences in prevalence are due to timing of transfusion, an important fact that was not analysed in the study. Before screening of blood donors for HBsAg, transfusions were much more likely to transmit hepatitis B. Patients with HCC were, on average, more than five years older than other individuals with chronic HCV infection, and were therefore more likely to have received HBV positive blood transfusions.

Dr Marusawa and colleagues' hypothesis may well be correct, and it has support from findings of other studies, quoted in their article, that have shown evidence of persistent HBV infection in HBsAg negative, anti-HBc positive individuals. Nevertheless, one should be cautious in accepting this hypothesis until all alternative explanations are ruled out.

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Reply

EDITOR,—As pointed out by Dr Nishioka, hepatitis B virus (HBV) can be transmitted via blood transfusion from infected donors or by injection using contaminated instruments, as is the case with hepatitis C virus (HCV) infection. Thus it may appear reasonable to consider that a high prevalence of HBV related serological markers in patients with HCV positive liver disease is due to simultaneous transmission of HCV and HBV. On the contrary, in patients with HCV related chronic liver disease, we could not find any correlation between anti-HBc positivity and various risk factors for blood borne infection, including previous history of blood transfu-

sion and intravenous drug abuse.¹ Furthermore, although the prevalence of anti-HBc increases as liver disease progresses, among patients with chronic hepatitis (CH), liver cirrhosis (LC), and hepatocellular carcinoma (HCC), the percentage with a history of blood transfusion was not markedly different. Therefore, we concluded that the high prevalence of HBV serological markers in patients with HCV related chronic liver disease was not correlated with their history of blood transfusion. We certainly appreciate the comments of Dr Nishioka suggesting that the differences in HBV seroprevalence among patients with CH, LC, and HCC may be due to the different timing of transfusion.

In fact, the mean age of patients with HCC was five years older than that of patients with CH or LC in our study population.¹ In Japan, screening of blood donors for hepatitis B surface antigen (HBsAg) was initiated 20 years ago, and since then occurrence of post-transfusion hepatitis B has dramatically decreased.² Thus those patients with HCC might actually have experienced a higher risk of receiving HBV positive blood transfusion than those with CH or LC. To address this possibility, we further investigated the seroprevalence of antibody against hepatitis B core antigen (anti-HBc) among our patients who had received blood transfusion before the start of HBsAg screening of blood donors. Even among the HCV positive patients who had received blood transfusion before screening began, the percentages of anti-HBc-positive cases were markedly different between patients with CH (85/192, 44.2%), LC (50/101, 49.5%), and HCC (68/119, 57.1%). Moreover, these percentages reflected those of the total population of patients with CH, LC, and HCC, irrespective of their blood transfusion history (43.8%, 49.8%, and 59.4%, respectively).¹

That said, we believe that the high prevalence of HBV related serological markers in HCV positive patients is not attributed to timing of blood transfusion. Unfortunately, when and how these anti-HBc positive patients were infected with HBV are not yet known. To this end, although the HBV genome is almost invariably present in the liver tissue of healthy subjects,³ whether or not this is also the case in patients with anti-HBc positive HCV related liver disease deserves clarification in future studies.

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Acid secretion in *H pylori* associated enlarged fold gastritis

EDITOR,—I was interested to read the elegant report of Murayama *et al* (*Gut* 1999;45:653-

661) demonstrating increased inflammation and abnormal parietal cell morphology and function in patients with *Helicobacter pylori* associated giant fold gastritis. However, the authors raise several points which deserve further comment.

The authors suggest that mediators of the inflammatory response may be important in inhibiting acid secretion and cite interleukin 1 β (IL-1 β) as the most important agent. It would be unwise not to consider other mediators. It is clear that IL-1 β has a variety of acid inhibitory actions; inhibiting gastric acid secretion when given both parenterally¹ and intracerebrally,² as well as having direct reversible inhibitory actions against both parietal cells³ and ECL cells.⁴ Thus locally produced IL-1 β may certainly be an important mediator of hypochlorhydria, indeed the same authors have previously shown that IL-1 β production in giant fold gastritis was negatively correlated with acid secretion.⁵ The authors have also demonstrated increased hepatocyte growth factor (HGF) production in giant fold gastritis,⁶ and although suggested to have a role in the fold enlargement, studies in canine parietal cells have shown potent acid inhibitory actions of HGF.⁶ Considerable data are available demonstrating that tumour necrosis factor α (TNF- α) is an important proinflammatory cytokine which is increased in *H pylori* gastritis; however, although there are no data specific to giant fold gastritis, it would be surprising if TNF- α expression were not increased. TNF- α also directly inhibits parietal cell acid secretion.⁷ Data on epithelial growth factor (EGF) and transforming growth factor α (TGF- α) and related peptides in *H pylori* infection are rather conflicting but there is evidence that expression is increased.⁷ These peptides are also potent inhibitors of parietal cell acid secretion,⁸ and transgenic over expression of TGF- α produces foveal hyperplasia and hypochlorhydria.⁹ Thus at present it would be wise to consider these and other possibilities as mediators of the reversible acid inhibition in *H pylori* associated acid inhibition.

Secondly, the authors believe that anti-gastric antibodies are not implicated in the pathophysiology of giant cell gastritis. They were unable to detect autoantibodies reactive with human gastric mucosa in any of their six subjects, but in the absence of more information on methodology and controls, the significance of these data remains uncertain. Negrini *et al* detected autologous and heterologous anti-gastric antibodies in 65% of *H pylori* infected patients, with an even greater prevalence with greater degrees of gastric inflammation (as seen in giant fold gastritis).¹⁰ Antigastric antibodies may be involved in the inhibition of acid secretion or may be merely a secondary phenomena following parietal cell damage. The data, as presented by Murayama *et al*, do not reliably exclude a pathogenic role for autoantibodies. Indeed if further larger studies confirm the absence of autoantibodies in giant cell gastritis, this will greatly facilitate our understanding of both the mechanisms of control of acid secretion in *H pylori* infection and generation of gastric autoantibodies.

Finally, the authors appear to regard the hypergastrinaemia of secondary consequence to inhibition of acid secretion. In light of this, it is unfortunate that they did not study a control group with drug induced secondary hypochlorhydria, as it is surely possible that some of the reversible parietal cell morphological changes result from

prolonged exposure to high levels of gastrin and gastrin precursors in the face of continued block of parietal cell function.

I look forward to further studies in this interesting patient group and hope that future studies will include appropriate controls to enable elucidation of the pathophysiology of giant cell gastritis.

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Reply

EDITOR.—We thank Dr Beales for the interesting comments on our paper.

The exact mechanism by which *Helicobacter pylori* infection induces decreased gastric acid secretion and alterations in parietal cell morphology remains unclear in patients with enlarged fold gastritis. One possible mechanism is that the cytokines produced by local immune system cells during inflammation may indirectly affect gastric function. Based on our previous finding that fundic mucosal interleukin 1 β (IL-1 β) production was enhanced in *H pylori* associated enlarged fold gastritis, it is suggested that IL-1 β was involved in the inhibition of acid secretion. As Dr Beales suggested, tumour necrosis factor α (TNF- α) is also one of the important cytokines in the inhibition of acid secretion. Unfortunately, we did not measure TNF- α levels in patients with enlarged fold gastritis, *H pylori* positive patients without enlarged folds, and *H pylori* negative patients with dyspeptic symptoms. However, we have previously demonstrated that macrophage infiltration in the body mucosa was significantly more extensive in patients with enlarged fold gastritis.¹ TNF- α is a cytokine which is produced mainly by activated

macrophages.² Therefore, we agree that TNF- α released by activated macrophages might also affect acid secretion in patients with enlarged fold gastritis. Thus the production of these cytokines, including IL-1 β , TNF- β , and others in inflamed mucosa might be equally important in the regulation of acid secretion in patients with enlarged fold gastritis. It is unlikely that transforming growth factor α (TGF- α) is involved in this pathophysiology, as we have previously reported that TGF- α mRNA levels in the body were not increased in patients with enlarged fold gastritis.¹

Dr Beales suggested the possibility that the presence of antigastric autoantibodies due to *H pylori* infection might affect the morphological and/or functional changes in parietal cells. As reported in our paper, however, the antigastric autoantibody in the sera of these patients with enlarged fold gastritis was undetectable, at least by our method. Faller *et al* reported that the occurrence of antigastric autoantibody, especially anticanalicular autoantibodies, correlates with the severity of body gastritis, and atrophic changes of the gastric mucosa.³ In our study, a significant difference in body atrophy score was not found among the six patients with enlarged fold gastritis, six *H pylori* positive patients without enlarged folds, or six *H pylori* negative patients. No significant change was observed in the degree of body atrophy after *H pylori* eradication in patients with enlarged fold gastritis. Thus it is also possible that antigastric autoantibodies do not necessarily exist in patients with enlarged fold gastritis. But when the gastric atrophy develops in future, antigastric autoantibodies may be detected in patients with enlarged fold gastritis. We feel that further larger investigations will need to clarify the pathophysiological significance of antigastric autoantibodies.

In our study, serum gastrin concentrations were correlated with morphological changes in parietal cells, as both elevated serum gastrin and morphological changes in parietal cells were found in patients with enlarged fold gastritis. Thus changes in the secretory canaliculi in parietal cells may possibly be due to differences in the degree of gastrin stimulation. However, it was reported that electron microscopic morphometry in normal subjects in a postprandial state or in patients with Zollinger-Ellison syndrome, which accompanied hypergastrinaemia, showed no significant alteration of parietal cells such as dilated canaliculi with vacuole-like structures and few short microvilli.⁴ Therefore, we think it is unlikely that the changes in the secretory canaliculi were due to differences in gastrin stimulation.

To resolve these issues, further analyses are needed in larger numbers of patients with enlarged fold gastritis, as Dr Beales suggested.

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Is there any relationship between IEL and lymphoid follicles in the gastric mucosa?

EDITOR.—The article by Hayat *et al* (*Gut* 1999;45:495-498) reporting the decrease in intraepithelial lymphocytes (IEL) in the gastric mucosa after *Helicobacter pylori* eradication is interesting and confirms the suggestion that lymphocytic gastritis could be a manifestation of an atypical host immune response to *H pylori*. But we would like to ask Dr Hayat and colleagues whether they also investigated the presence of lymphoid follicles in the lamina propria of gastric mucosa of their patients. In fact, mucosa associated lymphoid tissue (MALT), organised in follicles with a germinative centre and B cell reactivity, which structurally resemble Peyer's patches, can develop in the lamina propria after *H pylori* infection.^{1,2} Also, the development of these reactive lymphoid follicles may depend on the characteristics of the host and stimuli other than *H pylori*. We found lymphoid follicles in the gastric mucosa of 30% of our coeliac patients, of whom only 38% were infected with *H pylori*,³ supporting the hypothesis that the sensitivity of the host to various environmental factors (gliadin, *H pylori*, viral agents, other factors?) could be essential for the formation of lymphoid agglomerate.

In contrast, the functions of IEL remain a subject of speculation at present. They could be a reaction to abnormal antigen or an indication of abnormal regulatory mechanisms in the host. In some cases these cells have been shown to express CD4 whereas in others, CD8 cells predominate. However, they could play a part in negative regulation of the immune response or, alternatively, in B cell proliferation. Similarly, in the presence of lymphoma, they could represent an overflow of tumour associated T lymphocytes, necessary for the growth of the neoplasia.⁴ In summary, these IEL may participate in the process of B lymphocyte stimulation where abnormal antigenic stimulation probably plays an important part.

Dr Hayat, what is your opinion about the relationship between IEL and lymphoid follicles in the gastric mucosa?

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Reply

EDITOR,—This letter is the third from these authors on the subject of coeliac disease (CD) and gastric lymphoid follicles to be published thus far. Their first letter reported on findings in multiple gastric biopsies from 43 patients with CD.¹ Thirteen of the 43 (30%) had gastric lymphoid follicles but only five of these had *Helicobacter pylori* infection, the usual cause of acquired mucosa associated lymphoid tissue (MALT) in the gastric mucosa. Their second letter² speculated on the relationship between lymphocytic gastritis (LG), lymphoid follicles, and *H pylori* infection. The authors suggested that “the behaviour of *H pylori* positive lymphocytic gastritis after antimicrobial treatment should be further investigated”. Our report on such a trial³ has elicited a further letter in which Dr Cammarota and Professor Gasbarrini again speculate on the role of IELs in B cell proliferation and argue that such stimulation could lead to follicle formation and ultimately to B cell lymphoma (MALToma).

The key feature of LG is an increase in IELs above a threshold of 25 per 100 epithelial cells, and is therefore analogous to coeliac disease. In CD the most sensitive indicator of a response to treatment is a decline in the density of IELs. Thus we investigated IEL numbers as a measure of response in LG. Follicles are only an occasional histological finding in LG and are not considered to be part of the disease process. We did not therefore investigate the presence of follicles or their relationship to IELs. Indeed, we would go further and claim that there is no rational basis for undertaking such an exercise. B cell proliferation is a consequence of stimulation by activated CD4⁺ (helper) T lymphocytes mainly through cell-cell contact via the CD40 ligand. Small intestinal IELs are largely made up of CD8⁺ CD4⁻ T lymphocytes (that is, cytotoxic/suppressor phenotype). Although there are differences between gastric IELs in LG and CD, both the latter populations are largely made up (approximately 70%) of CD8⁺ cytotoxic/suppressor lymphocytes, with an even greater proportion of IELs expressing a cytoplasmic protein, TIA-1, which is a marker of cytotoxic potential.⁴ Thus few, if any, gastric IELs are of the CD4⁺ helper T cell phenotype. The role of IELs is not definitely known but there is nothing to suggest that they play a part in follicle formation or control of immunoglobulin synthesis.

Follicles are a prominent feature of *H pylori* gastritis where IEL counts are uniformly low. Indeed, follicles are particularly prominent in childhood infection where IEL counts are lower than in uninfected controls.⁵

Perhaps Dr Cammarota and Professor Gasbarrini can themselves suggest the mechanism by which IELs stimulate B cell proliferation and test their hypothesis by performing IEL counts and quantitation of IEL subtypes in gastric biopsies with and without follicles from their CD patients?

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hMLH1 and hMSH2 immunostaining in colorectal cancer

EDITOR,—The paper by Cawkwell and colleagues (*Gut* 1999;45:409-415) on the utility of hMLH1 and hMSH2 immunostaining in colorectal cancer may mislead the unwary reader just as it misled the author of the accompanying commentary (*Gut* 1999;45:325-326). Nowhere in their paper do the authors state that their approach will identify all cases of hereditary non-polyposis colorectal cancer (HNPCC). Nor would their method of ascertainment have picked up many HNPCC families. This is evident from the high proportion (83%) of cases with loss of hMLH1 while only four (apparently) of the 49 subjects with one or more RER positive colorectal carcinomas were diagnosed at less than 50 years of age. No subject was actually confirmed as having HNPCC. Yet the commentary states that the test showed that all HNPCC subjects had a deficit of either hMLH1 or hMSH2.

The test will certainly identify all sporadic RER positive or microsatellite instability-high (MSI-H) colorectal cancers in which the promoter region of hMLH1 is hypermethylated.¹ We found that 21/23 previously reported sporadic MSI-H cancers² showed loss of hMLH1. One showed loss of hMSH2. This subject was adopted as a child and developed his cancer at the age of 34 years. He probably had HNPCC. The other cancer retaining both hMLH1 and hMSH2 was on the borderline of MSI-L and MSI-H and had probably been assigned as MSI-H incorrectly. In contrast, none of 41 microsatellite stable nor 19 microsatellite-low (MSI-L) cases showed loss of hMLH1 or hMSH2.

The immunohistochemical approach will identify some but not all HNPCC cancers. The issues are as follows:

- (1) Genes other than hMLH1 and hMSH2 cause HNPCC.³
- (2) Subtly mutated proteins may retain antigenicity while losing function.³
- (3) Cancers in some HNPCC subjects may retain DNA repair proficiency.⁴
- (4) Not all HNPCC kindreds develop colorectal cancer.
- (5) Antigen retrieval may be technically difficult in old tissue blocks.⁴

It is essential that these caveats be understood before there is a major change in management strategy. A wider net is required to pick up all HNPCC families and this includes both routine morphological assessment and testing for DNA microsatellite instability as well as obtaining a family history on all subjects with colorectal cancer. Morphological assessment is not specific but costs little and will identify over 90% of HNPCC cancers regardless of microsatellite status or

mismatch repair protein expression status (unpublished observations).

Notwithstanding the words of caution, immunohistochemistry will serve as a major advance in the work up of suspected HNPCC families. It is particularly useful in identifying the underlying germline mutation and thereby facilitating genetic testing. The impact of the test on sporadic case management can certainly be anticipated but warrants further evaluation.

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Reply

EDITOR,—We are pleased that Professor Jass believes that immunohistochemistry will serve as a major advance in the work up of families with suspected hereditary non-polyposis colorectal cancer (HNPCC). We are also in absolute agreement that our immunohistochemical test is unlikely to detect all cases of true HNPCC. Our paper makes no claims to the contrary. The cases used in our study were subgrouped according to simple criteria such as patient age, and location and multiplicity of carcinomas. Our study design did not include a series of known HNPCC carcinomas and therefore we could not, and did not attempt to, state the value of the test in detecting true HNPCC carcinomas. Our main finding in the paper was the potential value in the sporadic setting of routinely staining all colorectal carcinomas using antibodies against hMSH2 and hMLH1. This would give information on prognosis, risk of metachronous colorectal carcinomas, and identify a group of patients who should be investigated further for HNPCC. However, the majority of cancers which exhibited loss of expression of the hMLH1 protein in our study are likely to be sporadic cases with hypermethylation of the hMLH1 promoter. It certainly would be important to assess the value of immunohistochemistry for the detection of true HNPCC cases but a large well characterised series with definite family history and known germline and somatic defects would ideally need to be assembled to fully answer this question. We have early data which suggest that the antibodies may have an important role and this is in preparation for submission as a paper.

The question of successful antigen retrieval from old tissue blocks is valid, but we have not encountered significant problems in further clinical series of 400 cases in the AXIS trial and 400 cases in the QUASAR 1 trial. Our paper mainly suggests the prospective assessment of all cases of colorectal cancer as they are diagnosed, therefore utilising new blocks.

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Reply

EDITOR,—I feel that Professor Jass misrepresents what I said in my commentary. I drew attention to the value of the method for detecting expression of the mismatch repair proteins MLH1 and MSH2 as a screening method for tumours showing deficient expression of one or other of these two proteins. I pointed out that there had not been a case of hereditary non-polyposis colorectal cancer (HNPCC) proved to be due to genetic loss of any other gene although there was a theoretical possibility that other genes could be involved. I did not state that the (immunohistochemical) test showed that all HNPCC subjects had a deficit of one of these two genes and I certainly did not say that by immunohistochemical staining for MLH1 and MSH2, all cases of HNPCC would be identified.

Jass has usefully widened the discussion about mismatch repair gene deficient colorectal cancers by drawing attention to his own validation of the morphological features of RER positive colorectal cancers.^{1,2} I agree that it is entirely possible that the immunohistochemical method could fail to identify every case of HNPCC, but it does have some degree of objectivity for detecting tumours with failed mismatch repair gene expression. Clearly, careful thought would need to be given to how this and other investigatory approaches should be applied if guidelines were to be produced for a national screening programme for HNPCC but the greater value of the immunological test may be in relation to management of patients with RER positive colorectal cancers.

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BOOK REVIEW

Proton Pump Inhibitors. Edited by Olbe L. (Pp 264; illustrated; sFr198.00.) Switzerland: Birkhäuser Verlag. 1999. ISBN 3 76435 897 1.

The history of the development of drugs to treat the so-called acid related diseases makes a fascinating story, and the publication of this book addresses a significant chapter in that story. Before 1976, treatment of peptic ulcer and gastroesophageal reflux disease was either inadequate medical therapy involving

antacids, non-selective anticholinergic drugs, or surgery with its associated morbidity problems. The advent of cimetidine (Tagamet), the first of the histamine H₂ receptor antagonists revolutionised the therapy of these diseases, and cimetidine became the first billion dollar drug. Subsequently, ranitidine (Zantac) superseded cimetidine as the world's most successful drug.

Despite their success, H₂ antagonists had some limitations, particularly in the treatment of gastroesophageal reflux disease and the arrival of omeprazole, the first proton pump inhibitor, with its profound and sustained inhibitory action on acid secretion represented a further significant therapeutic advance.

While the discovery of cimetidine was based on systematic pharmacological analysis aimed at a known target, that of the first proton pump inhibitors was serendipitous, their target and mechanism of action being initially unknown, and those early days are excellently described in the first chapter of this volume. The story of the antisecretory is often one of "what might have been", and this is illustrated by George Sachs in Chapter 2. He points out that SmithKline & French in Philadelphia instigated a programme for the regulation of gastric secretion by inhibiting the acid pump as early as 1968, but with the success of the H₂ antagonist programme in the United Kingdom, work was abandoned in 1973. Would history have been different if they had continued?

Chapter 1 ends on an enigmatic note, the final sentence stating that despite demonstration of clinical efficacy in the first trials of omeprazole described in 1982, "new problems were waiting round the corner". I assume this refers to the gastric carcinoid lesions found in long term toxicity tests on rat. At the time, this discovery generated genuine concern, and some hysteria, regarding the safety of proton pump inhibitors, and it certainly delayed the development and ultimate approval of omeprazole. However, the company involved, Astra, successfully convinced the regulatory authorities that it did not represent a problem for human studies, a position vindicated by the data presented by Werner Creuzfeldt in his key chapter. Interestingly, SmithKline & French and Glaxo took a different attitude when their long acting H₂ antagonists led to similar carcinoid formation and stopped their development programmes—was this the right decision? Concerns about sustained hypergastrinaemia caused by the prolonged inhibition of acid secretion by proton pump inhibitors also prompted the search for reversible K⁺ competitive H⁺/K⁺ATPase inhibitors, examples of which entered the clinic, but these too have been largely discontinued because of the efficacy and safety of available drugs.

Given the fact that omeprazole has been on the market for a decade, and in the light of its clinical and commercial success, it is surprising that this volume represents the first book to address the proton pump inhibitors, and I am pleased to say it fills that gap admirably. Lars Olbe has gathered together an excellent team of authors to produce a volume that is comprehensive (I cannot identify any aspect of the subject that is missing) and scientifically rigorous, but at the same time eminently readable for both the basic scientist and the clinician. History is dealt with, mechanisms of action made clear and understandable, clinical efficacy demonstrated, and the chapters on *Helicobacter pylori* bring us bang up to

date. In the socioeconomic section it would have been interesting to have some numbers (in ecus) to give an idea of the savings brought about by the use of proton pump inhibitors, but maybe this is unquantifiable. Most chapters have comprehensive bibliographies and the overall presentation of the book is good, although the index is a trifle thin—well, nothing can be perfect. It is difficult to judge the potential success of the book for a broad readership when the reviewer was actively involved in the field. As most reviewers say, I will certainly have this volume on my bookshelf, and it is not because I can keep my review copy.

M E PARSONS

NOTES

Joint Meeting of Oesophageal Section of the BSG and Association of Upper GI Surgeons

There will be a joint meeting of the Oesophageal Section of the British Society of Gastroenterology and the Association of Upper GI Surgeons exploring some important issues in oesophageal disease at the Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2 on Wednesday 1 November 2000. The meeting will take the form of four debates on:

- 1 The place of chemotherapy in the management of cancer of the oesophagus
- 2 The appropriate management of high grade dysplasia
- 3 Identifying the role of anti-reflux surgery in the current management of gastrooesophageal reflux disease and
- 4 The relevance of helicobacter pyloridis in oesophageal disease.

Further information from: WJ Owen, Hon Secretary, Oesophageal Section of the BSG, Suite 406 Emblem House, London Bridge Hospital, 27 Tooley Street, London SE1. Tel: (0)20 7403 3814; fax: (0)20 7403 3814.

17th World Congress, International Society for Digestive Surgery

The Society will hold its 17th World Congress in Hamburg, Germany on 6–9 September 2000. Further information from: Meetings Department, ISDS, 13 Elm Street, Manchester, MA 01944, USA. Tel: +1 978 526 8330; fax: +1 978 526 7521.

Frontiers in colorectal disease—A Multidisciplinary Approach

The above course will be held in London, UK on 16–18 October 2000. This year's Alan Parks Visiting Professor is Professor Guido Tytgat, University of Amsterdam. Further information from: The Administrator, St Mark's Academic Institute, Harrow, Middlesex HA1 3UJ. Tel: +44 (0)20 8235 4046; fax: +44 (0)20 8235 4039; email: e.power@ic.ac.uk; website: www.stmarkshospital.org.uk