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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 letter[2] 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 trial[3] 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 cancers[2] 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 H_2 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, H_2 antagonists had some limitations, particularly in the treatment of gastroesphageal 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 H_2 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 H_2 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; webstie: www.stmarkshospital.org.uk