

PostScript

LETTERS

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Distinction between "high grade MALT" and diffuse large B cell lymphoma

In order to communicate data about various lymphomas, it is necessary that we all speak the same language. To this end, many lymphoma classification schemes have been devised over the years. The most recent and current "official" lymphoma classification is that proposed by the World Health Organization (WHO).^{1,2} It differs very little from the previous "official" classification, the REAL (Revised European-American Lymphoma classification).³ Because the WHO classification is explicit, it is easy to follow and, if used correctly, studies using WHO terms should be reproducible and easy to interpret. However, when authors use language and classification schemes that are not widely accepted, they risk misinterpretation or that their data may be overlooked.

In the early 1980s, authors began referring to low grade B cell lymphomas that arise in mucosal locations as either "marginal zone" or mucosa associated lymphoid tissue ("MALT") lymphomas.^{4,5} Being the catchier of the two terms "MALToma" became dominant in the common parlance. However, this led to some confusion because the "MALT" descriptor has the connotation that there is only one type of lymphoma that arises in mucosal locations. In terms of biological behaviour however there are two common lymphomas that arise in mucosal locations, one indolent and one aggressive. As a descriptive rubric, the term "MALT" would encompass both entities and blur the line between them. This is one reason why the authors of the REAL and WHO classifications chose the term "extranodal marginal zone lymphoma" for the indolent entity—to distinguish it from diffuse large B cell lymphoma, the aggressive entity.^{1,3} The acronym "MALT" is fine for shorthand but should not be used without reference to the official name for the indolent neoplasm "extranodal marginal zone lymphoma".^{1,3}

In the paper by Nakamura and colleagues (*Gut* 2001;48:454-60), the authors use the terms "high grade MALT" and "low grade

MALT" without reference to official classifications. The use of such terminology is confusing, especially as the connotation of the materials and methods is that the authors called any lymphoma with large cells comprising "1% or more of the neoplastic population" a "high grade" lymphoma. In response to my inquiry about this problem, published on the *Gut* website, the authors partially cleared up this confusion by explaining that in order to be considered a "high grade MALT" in their study, a lymphoma must contain 10% large cells. One problem with this scheme is that typical low grade "MALT" lymphomas usually contain benign germinal centres composed of sheets of large cells in the background. Did the authors specifically look for and exclude benign germinal centres in their classification? Also, the percentage of large cells in each case is not provided in the paper.

Moreover, the WHO classification explicitly states that marginal zone lymphomas should not be graded.^{1,2} Large cell lesions such as those depicted by Nakamura *et al* in their online response should be referred to as "diffuse large B cell lymphoma." In that online response, the authors state that "our cases with high grade MALT lymphoma were categorised into diffuse large B cell lymphoma plus areas of marginal zone/MALT lymphoma". Again, this is confusing because the REAL/WHO classification terms "marginal zone lymphoma" and "diffuse large B cell lymphoma" were not used in the paper.

In closing, one important point should be reiterated: in order for readers to derive meaningful information from lymphoma studies, those studies must use widely accepted lymphoma classification terminology. In studies where deviation from such terminology is necessary, the materials and methods must explain the classification scheme precisely and explicitly.⁶

Are Nakamura *et al* saying that gastric diffuse large B cell lymphoma can be cured by anti-*Helicobacter pylori* therapy?

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Authors' reply

In our paper (*Gut* 2001;48:454-60), the recently proposed WHO classification of lymphoid neoplasms¹ was not applied as our study was conducted during the period 1994-1998, and our manuscript was submitted in 1999. As we have previously responded to Dr Ely on the *Gut* website, the five cases with high grade mucosa associated lymphoid tissue (MALT) lymphoma in our study were categorised as diffuse large B cell lymphoma plus areas of marginal zone/MALT-type lymphoma, according to the WHO classification. The percentage of neoplastic large cells in these five cases was as follows: 30% and 40% each in two cases which regressed after eradication of *Helicobacter pylori* and 30%, 70%, and 90% each in three cases which did not respond to eradication therapy. It took for granted that reactive germinal centres were not overestimated.

To date, more than 20 cases of gastric diffuse large B cell lymphoma with or without areas of low grade MALT lymphoma have been reported to have regressed after *H pylori* eradication.²⁻¹⁰ Based on these observations, we consider that high grade MALT lymphoma/diffuse large B cell lymphoma with areas of marginal zone lymphoma in the early stage possibly responds to *H pylori* eradication. To determine whether or not patients with a response to *H pylori* eradication relapse in the future, a longer follow up study in a large number of patients would be necessary.

In addition, recent publications have shown that gastric diffuse large B cell lymphoma with areas of marginal zone lymphoma (high grade MALT lymphoma in our classification) had a better survival compared with that without evidence of MALT lymphoma.¹¹⁻¹³ Many investigators still use the term "high grade MALT lymphoma".^{4-6,11} Whichever term is accepted widely in the future, we believe that gastric diffuse large B cell lymphoma with areas of marginal zone lymphoma should be distinguished from that without MALT lymphoma.

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Mortality with oesophageal varices: different things to different people

LeBrec (*Gut* 2001;**49**:607–8) has summarised reports showing that mortality from bleeding varices has significantly decreased in the past few decades. Because of the limited follow up in some of these publications, we have examined the published mortality from bleeding varices where follow up data were available for at least one year (group BV). For comparison, similar data were collected from studies in patients with known varices who had not bled (group NBV).

For inclusion, patients had to be reported in a randomised controlled trial, published in full between 1984 and 2001. Management under the protocols had to be initiated promptly and survival data had to be recorded for at least one year. The few patients reported as transplanted were counted as survivors. In most instances there was no statistical difference in survival between treatment arms and the data were combined. Where this was not the case (three in the BV group and four in the NBV group) only data from the treatment arm showing better survival were included in the analysis.

Table 1 Mortality (%) in patients with bleeding varices (group BV) compared with those in patients with known varices who did not bleed (group NBV)

	Group BV	Group NBV
Year 1	24.9 (4.40)	19.5 (1.80)
Range	7.4–64.2	6.2–39.7
Year 2	32.2 (6.50) (n=9)	31.4 (3.45) (n=18)
Range	14.7–71.1	9.6–52.6
Year 3		46.0 (7.31) (n=9)
Range		16.9–80.2
Year 4		56.5 (8.33) (n=6)
Range		33.6–82.7

Thirteen publications in the BV group representing 1321 patients of mean age 53.4 (SEM 1.13) years met the inclusion criteria. The NBV group comprised 2472 patients of mean age 54.9 (0.90) years. Mortalities are shown in table 1.

There was no statistically significant difference in mortality between the BV and NBV groups for the two years for which comparisons were possible. There was no correlation between mortality and the number of patients included in each report or the date of publication.

These data show that patients with oesophageal varices, although in their mid-fifties, have a life expectancy of normal individuals in their mid-eighties. The presence of varices, whether they have bled or not, is an ominous prognostic sign regardless of how they are treated.

There are limitations to this analysis. The prevalence of varices is not known. The fate of patients who die before reaching a treating facility or where the outcome is unreported is also unknown. Yet, as pointed out by Graham and Smith,^{1,2} the timing of randomisation for any treatment programme has a major impact on outcome. Again, the relatively large number of patients included in this analysis and the wide range of mortalities reported may obscure real differences in as yet unidentified subgroups. None the less these data are sobering. As pointed out by Smith and Graham more than 20 years ago, "...we have learnt much and accomplished little".¹

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Cytokeratin immunoreactivity of intestinal metaplasia

We read with great interest the well designed study of Couvelard *et al* (*Gut* 2001;**49**:761–6). In agreement with other studies,^{1,3} the authors reported that cytokeratin (CK) 7 and 20 immunoreactivity in the specialised intestinal metaplasia found in Barrett's oesophagus differs from the intestinal metaplasia found in the stomach. The specific pattern of CK7/CK20 expression, so-called Barrett's type, is characterised by strong CK7 staining of both superficial and deep glands together with a

strong superficial CK20 stain. The authors report that both clinical and endoscopic findings support this differentiation.

The origin and development of intestinal metaplasia at the gastro-oesophageal junction have been a matter for debate. There are findings suggesting that intestinal metaplasia of the cardia has an immunophenotype similar to Barrett's oesophagus³ while others suggest that it is similar to the rest of the gastric mucosa.¹ We evaluated the CK7/CK20 pattern of gastric cardia with intestinal metaplasia and compared it with Barrett's oesophagus, corpus, and antrum metaplasia in 68 endoscopic biopsies and selected surgical specimens.⁴ Immunostaining was performed using the same monoclonal antibodies for CK7 and CK20 as in the study of Couvelard *et al* for all specimens of Barrett's (n=17), cardia metaplasia (n=15), corpus metaplasia (n=14), and antrum metaplasia (n=22).

We found three patterns of CK7/CK20 immunostaining and identified them as IM-1, IM-2, and IM-3. IM-1 is characterised by strong diffuse CK7 staining in both superficial and deep glands and strong superficial CK20 immunostaining, corresponding to the so-called Barrett CK7/CK20 pattern. IM-2 is characterised by either negative or weak patchy CK7 staining of the surface and crypt epithelium and a strong diffuse surface epithelium and patchy crypt CK20 staining (corresponding to the so-called gastric CK7/CK20 pattern). IM-3 pattern is characterised by strong and patchy CK7 staining of the surface and crypt epithelium and strong diffuse surface and patchy crypt CK20 immunostaining. Sixteen of the 17 cases with long segment Barrett's oesophagus (94%) and one of the 15 cases with cardia metaplasia expressed the IM-1 CK7/CK20 pattern. The IM-1 or Barrett's CK7/CK20 pattern had a high specificity as none of the 36 cases representing intestinal metaplasia of the corpus and antrum had this immunostaining pattern. The IM-2 pattern was present in most of the specimens with intestinal metaplasia in the stomach (34 of 36) (table 1).

We hypothesise that the differences in the immunophenotypes observed in intestinal metaplasia of the cardia are mainly associated with different practices in collecting biopsy samples. As in the study of Couvelard *et al*, we paid particular attention so as to have the mucosal biopsies directly across from the Z line by adequately positioning the biopsy forceps. None the less, biopsy samples taken less than 1 cm proximal to the gastric folds could actually represent "short segment Barrett's oesophagus" in some cases.^{5,6} As stated by the authors, no absolute histological criteria for diagnosing Barrett's mucosa have yet been established. Therefore, it would be interesting to know the types of epithelium that were

Table 1 Distribution of CK7/CK20 immunostaining patterns in long segment (LS) Barrett's oesophagus, cardia, corpus, and antrum intestinal metaplasia (IM)

CK pattern	LS Barrett (n=17)	Cardia IM (n=15)	Corpus IM (n=14)	Antrum IM (n=22)
IM-1	94%	7%	0%	0%
IM-2	6%	80%	100%	91%
IM-3	0%	13%	0%	9%

revealed on the gastric side of the Z line (cardiac, fundic, or perhaps specialised columnar epithelium).

There is sufficient evidence to suggest that "Barrett's CK7/CK20 pattern" is a useful tool in distinguishing between Barrett's oesophagus and intestinal metaplasia of the cardia. However, more research is needed for a better understanding of the development and meaning of intestinal metaplasia of the cardia.

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Authors' reply

We thank Mouzas *et al* for their comments on our study. We read with interest their results that are partly in keeping with our data and that confirm that Barrett's mucosa has a specific pattern of cytokeratin (CK) expression. Two comments can be made with respect to

this work. Firstly, we have noticed that the authors identified three CK7/20 patterns of intestinal metaplasia (IM-1, IM-2, and IM-3). Although IM-1 is identical to that designated as Barrett's pattern by Ormsby *et al*, it is important to note that IM-2 and IM-3 do not strictly parallel the two other CK7/20 patterns defined by Ormsby *et al* as corresponding to the gastric type of intestinal metaplasia.¹ Thus the significance of IM-2 and IM-3, as proposed by Mouzas *et al*, have still to be clarified. In the small areas of intestinal metaplasia that are found in biopsy specimen from the gastro-oesophageal junction, we have made the distinction between the typical "Barrett's phenotype" (as described by Ormsby *et al* and corresponding to IM-1 type) and other types that we have considered as "gastric phenotypes". Secondly, Mouzas *et al* identified only one case of Barrett's type intestinal metaplasia among 15 cases of cardiac intestinal metaplasia, suggesting that intestinal metaplasia of the gastro-oesophageal junction is only rarely related to short segments of Barrett's oesophagus. This finding is not consistent with our results in that we found 16 patients presenting with Barrett's CK7/20 pattern among 34 patients that were evaluated for immunohistochemistry. However, this discrepancy may be related to the limited collection of biopsy samples and may be influenced by *Helicobacter pylori* status, age, sex, and ethnic origin of the patients, data that were not reported in the present work of Mouzas *et al*.

At the end of their letter, Mouzas *et al* question the type of epithelium that we found on the gastric side of the gastro-oesophageal junction. As the site of biopsy sampling may be critically important, we reviewed all gastro-oesophageal junction biopsy specimens for histological evidence of the squamo-columnar junction. Among the 988 biopsy specimens corresponding to the 254 patients with an endoscopically normal gastro-oesophageal junction included in our study, 382 (39%) containing both squamous and columnar epithelium were considered as directly taken across the Z line. Cardiac mucosa was present in 373 of the 382 biopsy specimens (97.6%), in association with fundic mucosa in 74/373 cases (19.8%). In nine of 382 biopsy specimens (2.4%) there was only fundic mucosa. Moreover, we found the same ratio when patients were divided into two groups, one group corresponding to 60 patients with intestinal metaplasia at the gastro-oesophageal junction (116 biopsy specimens across the Z line, containing cardiac mucosa in 113 (97.4%) in association with fundic mucosa in 18/113 (15.9%) and containing only fundic mucosa in 3 (2.6%)) and the other group corresponding to 194 patients without intestinal metaplasia at the gastro-oesophageal junction (266 biopsy specimens across the Z line, containing cardiac mucosa in 260 (97.7%) in association with fundic mucosa in 56/260 (21.5%) and containing

only fundic mucosa in 6 (2.26%)). These data, in line with those obtained in an autopsy series, support the concept that the gastric cardia is present as a constant structure.² However, it must be remembered that some workers recently proposed the hypothesis that cardiac-type mucosa arises as a metaplastic phenomenon.³

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Serrated adenomas in FAP

We read with interest the article by Matsumoto *et al* reporting their observations on the presence of serrated adenomas in familial adenomatous polyposis (FAP) patients in relation to germline APC mutations (*Gut* 2002;**50**:402-4). Their small colonoscopic study identified three FAP patients with serrated adenomas; all had less than 100 polyps and they concluded that serrated adenomas may be characteristic of attenuated FAP.

It is our practice to perform prophylactic colectomy with ileorectal anastomosis or ileoanal pouch formation in patients with FAP in the second or third decade or as soon as possible after a new diagnosis is established. An expert histopathologist performs a meticulous examination of the colectomy specimen, including a formal polyp count. Thereafter any rectal remnant is surveyed six monthly by flexible sigmoidoscopy with endoscopic snare polypectomy and argon plasma coagulation of suspicious lesions.

A simple search of the St Mark's polyposis registry has revealed eight patients in whom serrated adenomas have been identified. In five patients the lesion was present in the colectomy specimen, in two the diagnosis was

Table 1 Patient characteristics of eight patients in whom serrated adenomas were identified in St Mark's polyposis registry

Patient No (sex)	Age at colectomy (y)	Preoperative endoscopy	Colectomy specimen polyp count	Site and size of serrated adenoma	APC mutation analysis
1 Male	29	Not available	3550	Sigmoid colon 1.2 cm (colectomy)	Ex 15 4175 c >g
2 Female	36	Classical FAP	1230	Descending colon 0.5 cm (colectomy)	Under investigation
3 Male	19	Low polyp count	Not available	Rectum 0.5 cm (colectomy)	Unsuccessful
4 Female	39	Classical FAP	900	Rectal polyp (surgical excision)	Unsuccessful
5 Female	17	Classical FAP	648	Descending colon (colectomy)	Ex 15 2367-2368 deletion
6 Male	19	Low polyp count	868	Rectal biopsy	Unsuccessful
7 Male	19	Classical FAP	Hundreds	Rectal biopsy	Ex 15 3254-3257 del
8 Female	14	Not available	1425	Colectomy specimen	Unsuccessful

FAP, familial adenomatous polyposis.

made on flexible endoscopic surveillance, and in one case a serrated adenoma was present in a polyp surgically excised from the rectum (table 1).

As in Matsumoto's study, in the majority of the St Mark's cases the serrated adenoma was located distally either in the sigmoid colon or rectum. However, in our patients serrated adenomas were not restricted to those with the attenuated phenotype. Seven of the St Mark's patients with serrated adenomas have classical FAP with more than 100 colonic polyps in the colectomy specimen. (In one of these patients preoperative colonoscopy reported a low polyp count.) The genetic mutations have been identified in three of our patients and all were in exon 15, rather than more proximally.

Serrated adenomas may be a feature in FAP but they are not characteristic of the attenuated phenotype. Colonoscopy alone may underestimate the number of colorectal polyps, especially in difficult cases. We believe that dye spray colonoscopy by an experienced endoscopist and careful examination of colectomy specimens are necessary to completely characterise the FAP phenotype.

The clinical significance of the presence of serrated adenomas in FAP patients has yet to be determined. Further studies in this interesting area are required.

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Authors' reply

We would like to thank Drs Gallagher and Phillips for their comments on our article. They raise the point that experienced colonoscopists should assess colorectal lesions in familial adenomatous polyposis (FAP) using a dye spraying technique. It has been shown previously that conventional colonoscopy would underestimate the number of adenomas in patients with attenuated FAP.¹ In two of the three subjects with polyps less than 100 in number, chromoscopy identified numerous and diminutive areas of flat configuration in the colorectum where tubular adenomas were confirmed histologically. While chromoscopy identified numerous non-polypoid areas of tubular adenomas in two of the three subjects with serrated adenomas, their sparse colorectal polyposis and the APC gene mutation were compatible with FAP of the attenuated form.^{2,3}

Another important issue raised by Drs Gallagher and Phillips is the fact that in their

histological survey of resected specimens three patients with serrated adenomas had an APC mutation at the proximal part of exon 15. This discrepancy may have arisen from differences in the procedure of assessment for colorectal adenomatosis. In our 15 colectomised specimens of FAP however, we have not yet found any serrated adenomas. Based on the comments of Drs Gallagher and Phillips, other colectomised specimens are under investigation at our institute. Until many more patients with FAP or attenuated FAP are identified, the correlation between serrated adenomas and the genotype of FAP remains controversial.

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Timing and sampling in surveillance of premalignant gastric lesions

We read with interest the paper by Whiting *et al* (*Gut* 2002;**50**:378–81) regarding the surveillance of premalignant gastric lesions. The authors reported that over 10 years, 12 cancers (11.5%) were diagnosed in 104 patients with intestinal metaplasia and/or atrophic gastritis. Therefore, they suggest that these patients have an increased risk of developing gastric cancer, and benefit from annual endoscopic follow up.

Although we agree with the major conclusions of the study, our experience is somehow different. In fact, we have recently investigated the timing of first endoscopic-histological follow up of patients with body predominant atrophic gastritis and demonstrated that four years seems a satisfactory interval for the first follow up of these patients.¹ The timing of surveillance should be safe enough not to miss malignancies at early stages but very close follow up may affect

compliance. In fact, Whiting *et al* underlined how the proposed annual surveillance protocol was accepted by less than 50% of their patients. Thus it may be speculated that a number of cancers equal to those diagnosed may have been missed. In our population compliance was similar among patients who had follow up proposed at two or four years (73% v 64.5%), and we found no malignancies at the two year follow up, with only one carcinoid tumour at four years, despite a detailed histological sampling, including an accurate evaluation of ECL cell patterns.¹ In fact, we have demonstrated that this approach can address further evaluations for patients at high risk of developing carcinoid tumours.² Unfortunately, in Whiting's paper the time interval from the diagnosis of atrophy and/or metaplasia to that of cancer is not clearly reported, making comparisons difficult, given also the lower number of our patients and the different ethnicities.

Furthermore, while we evaluated only patients with atrophy and metaplasia of the gastric body, in Whiting's paper histological details are not given. It is well known that the diagnosis of atrophic gastritis is difficult, with poor agreement even among expert pathologists and it has been recommended to diagnose "atrophy" only when appropriate gastric glands are replaced by intestinal epithelium or by fibrosis.³ Therefore, as the authors state that patients were included in the group at higher risk when more than one risk factor was present, we assume that all intestinal metaplasia patients had atrophy also. The number and site of biopsies needed to define the topography of atrophy and metaplasia in the antral or corporal mucosa are also important. In fact, it has been demonstrated that corpus predominant gastritis related hypochlorhydria is a key factor in the multistep carcinogenesis cascade.⁴

Moreover, in Whiting's study, *Helicobacter pylori* infection was not mentioned, even in patients enrolled between 1984 and 1988 and followed annually for 10 years, a period in which it has become widely accepted that patients with *H pylori* infection and premalignant changes deserve antimicrobial therapy,⁵ even if the possible effect of *H pylori* cure in premalignant conditions is still a matter of discussion.⁶

It would therefore have been interesting to know whether in Whiting's study malignancies at follow up occurred more frequently in patients with atrophic changes and metaplasia in the gastric body or in those who were *H pylori* positive, but these data were not provided.

In conclusion, while we agree that surveillance of patients with atrophic gastritis is an important goal that deserves attention, we believe that other large prospective studies are

needed to establish the best timing of follow up and histological protocols to optimise resources and join compliance and early diagnosis of gastric malignancies.

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Coeliac disease and the risk of autoimmune disorders

We recently suggested in a study on 909 adolescent and young adults aged 15+ years (mean 16.1) that the prevalence of autoimmune diseases in coeliac adults is related to the length of gluten exposure, independently of the expected age effect.¹ Recently, Sategna Guidetti *et al* (*Gut* 2001;**49**:502–5) presented a paper which, in the title itself, negates this hypothesis.

However, we feel quite happy with the contribution of Sategna Guidetti *et al* as we found strong confirmation of our findings in their paper. As mentioned by the authors, their paper stimulates some interesting observations.

(1) The population they studied was affected by a very strong "age" selection as the vast majority were aged over 40 years and hence all had maximum exposure to the risk factors (100% had been exposed to gluten for >20 years, including "actual gluten exposure") and there was no modulation of effect, just the end point, which surprisingly was identical to our own results. We have not studied a paediatric population, but young adults with a mean age of 16.7 years and the risk factor was evaluated over the whole range of ages before the outcome (autoimmune disease) was expected.

(2) "Age at diagnosis" is a robust variable and is unlikely to be biased. Sategna Guidetti *et al* showed, very consistently, that age at diagnosis was related to outcome. The actual prevalence of autoimmune diseases was even higher than that observed by us (possibly due to age range?).

(3) The variable "actual gluten exposure", artificially built by the authors, was largely based on age at diagnosis (hard data) together

with minor components related to self reported compliance and follow up.

(4) In summary, if they included in a multivariate model the strong variable "age at diagnosis" which explains a significant part of the variance in the outcome variable, it is very unlikely that a second variable (supposed "actual gluten exposure") containing the first strong variable adds any further contribution to the outcome variable.

(5) One important prerequisite for a multivariate model is to include variables independent of each other, which was definitely not the case here. In the logistic regression model the variables included were the "strong" ones, as expected in this type of analysis. The outcome (prevalence of autoimmune diseases) was significantly related to present age and age at diagnosis of coeliac disease. What else could contribute to the derived variable "actual gluten exposure"?

To add strength to this finding, we have new prospective data from a cohort of 74 coeliac patients (46 females) diagnosed before the age of five years and followed up for an average period of 18.4 years (range 10–30); their actual mean age is now 20.34 years. Of these, 5/74 developed an autoimmune disease during this follow up period (two dermatitis herpetiformis, one thyroiditis, one MMC, one psoriasis): all of these cases had been exposed to a gluten challenge for 11–48 months after a variable length of time on a gluten free diet. These indeed had "gluten exposure", unfortunately added on a relatively precocious diagnosis. None of the other 69 patients has developed an autoimmune disease to date.

We thank our colleagues for their significant confirmation to our findings and hope that they will share our will to explore the biological reasons which may explain why age at diagnosis is so strongly correlated with the prevalence of autoimmune diseases in adults.

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Authors' reply

We thank Ventura *et al* for their comments on our paper, and we are delighted to have made them happy, but we would like to clarify a few points.

As underlined in our article, we believe that the conclusions of the two papers are not to be considered antithetical for the following reasons.

(a) They were conducted in different coeliac disease (CD) age groups and, as underlined by Londei in his commentary on our article,¹ "to date there is no consensus that child and adult CD are the same condition, nor that subjects in whom CD has been diagnosed in adulthood have had CD all their life".

(b) Study designs were different. In Ventura *et al*'s survey, actual age between 10 and 25 years was the only selection criterion; CD patients,

consecutively recruited over a six month period from 10 paediatric gastroenterology centres, were grouped according to age at diagnosis into three sets: 374 diagnosed before two years of age, 276 diagnosed between two and 10 years, and 259 diagnosed after 10 years of age. Patients who underwent a gluten challenge for diagnostic purposes and its duration were recorded, while neither diet compliance (it is well known that many teenagers are non-compliant!) nor intestinal mucosa outcomes were mentioned. Conversely, in our study, only patients in whom CD had been diagnosed at our centre, at age ≥ 16 years (range 16–84), who had been in clinical remission for at least one year, and whose compliance with the diet was ascertained not only by direct enquiry but also by histological outcome of intestinal lesions entered the study: only 422/713 met these stringent inclusion criteria.

(c) When considering an adult versus a paediatric population, we should be aware of a possible screening bias due to different clinical suspicions and presentations.

(d) Although "the conclusions at first glance seem to be similar in the two reports" concerning age at diagnosis as a risk factor, this cannot be viewed as a "surprising" confirmation of Ventura *et al*'s study hypothesis. Rather this should suggest the application of the "actual gluten exposure" concept to their population, as also proposed by Londei.¹

The "strong" age at diagnosis variable can be biased by screening procedures and medical awareness directed to both coeliac and autoimmune (AI) diseases when faced with silent or oligosymptomatic patients.

The "artificially built variable" actual gluten exposure may be perceived with difficulty by a cursory and hasty reading. It is not a "self reported compliance and follow up" but provides a better indication of the effective gluten exposure as it takes into account not only age at CD diagnosis but also age at diagnosis of AI disorders. The beginning of a strict gluten free diet in patients in whom recovery of intestinal lesions was ascertained by histological findings (and not only by self reported compliance, as Ventura *et al* seem to have gathered), was considered as the end time of gluten exposure. In other words, the period of gluten exposure matched the time of AI disease onset in patients in whom AI disease preceded CD diagnosis, and the beginning of gluten withdrawal (with ascertained compliance by means of the above mentioned criteria) in patients in whom a CD diagnosis was made before AI disease onset, respectively.

Thus when adult CD patients with and without AI associated diseases were compared, age at CD diagnosis, considered as an indirect mirror of duration of gluten exposure, was significantly higher in patients with associated AI disorders, while actual gluten exposure was similar in both groups; moreover, in 35% of patients an AI disease appeared after a diagnosis of CD, even in subjects in whom recovery of intestinal mucosa was ascertained.

This fact and the finding of a 30% prevalence of AI disorders in our patients aged 41 (± 15) years compared with 23% in Ventura *et al*'s study in patients aged 16 (± 3.8) years (unless there was a recent revision of which we are unaware, paediatric age comprises adolescence and up to 18 years of age), raises critical questions on the relationship between CD and AI diseases.

The variable "actual gluten exposure" not only reflects more accurately the duration of gluten exposure but eliminates weighty confounding factors that contribute strongly to the apparently significant relationship between age at diagnosis and outcome in the logistic regression model.

In CD, there is a generalised increase in permeability to macromolecules, making it likely that Peyer's patches are not the only site where gliadins are in contact with the immune system. Gluten peptides may encounter the gut immune system in a fashion that bypasses the normal controlled sampling, leading to sensitisation or loss of tolerance to the antigen.

Despite their diverse aetiology, certain pathogenetic mechanisms are common to all AI diseases: as a rule, they require the presence of self reactive CD4 positive T lymphocytes which are believed to be deleted in the thymus and to be present only when they arise following somatic mutation, producing "forbidden clones".

The question is why only a minority of CD patients manifest an AI disease?

Most AI diseases show a particular bias for certain HLA haplotypes, usually belonging to class II, which encodes important immune response regulating genes: thus some rational connection may exist between the genetic constitution and susceptibility to AI disorders.

CD seems to meet the criteria of a true AI disease triggered by an environmental agent (gluten) in genetically predisposed individuals. It has been estimated that the HLA contribution to the development of CD among siblings is 36%³ and recent data suggest that a gene or genes other than the HLA unlinked locus must also participate and are likely to be stronger determinants of disease susceptibility than the HLA locus.^{4,5} The non-HLA locus appears to be inherited as an autosomal recessive trait.⁶

This may suggest that exposure of the immature system to gliadin in susceptible individuals is a prominent cofactor in modifying the immunological response earlier in life and thus predisposing susceptible individuals, not only to overt CD, but also to AI diseases. In other words, "les jeux sont fait" early in life.

Thus the search for genetic characteristics of CD patients with associated AI diseases could be much more stimulating than meaningless controversies.

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Non-alcoholic steatohepatitis (NASH): why biopsy?

The leading article by Day (*Gut* 2002;**50**:585–8) provides a valuable summary of the current understanding of the pathogenesis and clinical relevance of non-alcoholic steatohepatitis (NASH). The article also makes two points clear: (a) we have little ability to provide accurate prognostic information in an individual patient, even when liver histology is available, and (b) although there is the promise of new treatments, the only known effective therapy at present, for the obese patient, is weight loss. Why then should these patients be subjected to liver biopsy?

Day proposes that a subgroup of patients with suspected fatty liver should undergo biopsy, including those with alanine aminotransferase (ALT) more than twice the upper limit of normal, aspartate aminotransferase >ALT values, "moderate" central obesity, non-insulin dependent diabetes, hypertension, and hypertriglyceridaemia. Gastroenterologists are commonly referred patients fulfilling these criteria but is liver biopsy likely to affect their management? The only therapeutic option at present is weight loss and all obese patients should of course lose weight, whether they have simple steatosis, NASH, or even normal liver biochemistry.

A number of arguments may be used to justify liver biopsy in these patients; histopathology may reveal unexpected findings and the results may allow more accurate prognostic information to be given to the patient.

Sherwood and colleagues¹ identified 342 patients found on screening by their general practitioner to have liver enzymes raised above twice the normal upper limit who had not been referred to a specialist for further assessment. Of these, less than half were thought to require further investigation, approximately one third of whom had normal results on repeat testing. Following investigation of the remainder in a gastroenterology clinic, alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) accounted for 43% and in nearly all of the others a diagnosis could have been reached with the aid of careful history taking (alcohol and drugs), serological testing (viral hepatitis, markers of iron overload, primary biliary cirrhosis, α_1 antitrypsin deficiency), and ultrasound examination (common bile duct stones). These data would suggest that biopsy for those with raised liver enzymes rarely yields an unexpected diagnosis and can be reserved for a selected subgroup of patients following non-invasive testing. None of the patients with NAFLD were cirrhotic on biopsy, although 11 (42%) had fibrosis. The results of liver biopsy would not have affected the clinical management of the small number of patients with unexpected histological findings; six patients had "autoimmune" or "cryptogenic" hepatitis, but assuming transaminase levels were only approximately twice the normal upper limit there would be no justification for immunosuppressive therapy.

It is difficult to justify liver biopsy simply to provide the patient with better prognostic information. Patients with marked fibrosis are more likely to develop cirrhosis and die from liver disease² but it is not yet clear that patients with simple steatosis and mild fibrosis can be reassured they will not, in time, develop more severe liver disease.

Most gastroenterologists, particularly those who work in district general hospitals, adopt a

pragmatic approach to the management of patients referred with abnormal liver biochemistry. This is especially important for investigations that are costly and/or are associated with significant morbidity, as with liver biopsy.³ The presence of cirrhosis will affect patient management but, as Day points out in his article, published cirrhosis rates in NAFLD are likely to be overestimates because most studies have not been done on unselected patient groups. Improved criteria for selecting patients likely to have marked fibrosis or cirrhosis are required to target biopsies more appropriately.

When effective medical treatments are available, clear criteria for liver biopsy should follow. Until then, liver biopsy in the majority of these patients outside a research setting cannot be justified.

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Author's reply

In his letter, Dr McNair states that liver biopsy is not justified in patients with suspected non-alcoholic steatohepatitis (NASH) outside a research setting. His principal arguments are that liver biopsy is unlikely to: (a) improve diagnostic accuracy, (b) provide more accurate prognostic information, and (c) effect management.

To support his first argument, Dr McNair cites a study which examined whether abnormal liver function test results are investigated appropriately in primary care and reported on the eventual diagnosis after full investigation.¹ I am sure that the authors of this study would be surprised at this use of their data by Dr McNair both in view of the inaccuracies present in the citation and the conclusions drawn. For example, contrary to McNair's letter, just over 20% (36/157) of patients thought to require further investigation had normal results on repeat testing and in the remainder, 56% (68/121) rather than 43%, had alcoholic liver disease or non-alcoholic fatty liver disease. Contrary to McNair's statement that: "These data would suggest that biopsy for those with raised liver enzymes rarely yields an unexpected diagnosis and can be reserved for a selected group of patients following non-invasive testing", the cited report states that: "Liver biopsy provided a diagnosis in 81 (patients) when serological tests gave normal results". Furthermore, contrary to McNair's statement that liver biopsy did not effect clinical management, the cited report states that: "Of these 157 patients, 97 (62%) had an identifiable diagnosis requiring hospital intervention or follow-up or both". Therefore, the cited report suggests strongly that liver biopsy is useful for diagnosis in patients with negative serology and that the eventual diagnosis has implications for management. Specifically referring to NASH, further evidence of the utility of liver biopsy for diagnostic reasons comes from a study in which a group of eminent hepatologists were

given clinical and laboratory data on a variety of different "liver" patients and asked to predict the correct diagnosis without knowledge of the findings on liver biopsy.² Compared with other liver diseases the clinical diagnosis of NASH was the most inaccurate.

Even if I accepted Dr McNair's argument that the diagnosis of non-alcoholic fatty liver disease (NAFLD) can be made on clinical grounds, it would be difficult to agree with his second argument that liver biopsy does not provide the clinician and patient with more accurate prognostic information. The study by Matteoni and colleagues³ along with our own study⁴ showed that, over at least a 10 year follow up period, patients with simple steatosis are highly unlikely to progress to more advanced disease whereas approximately 25% of patients with NASH with or without fibrosis will progress to cirrhosis within eight years. I agree with Dr McNair that further natural history studies are required but I consider that the information available at present allows clinicians to give patients with simple fatty liver a good prognosis and, importantly, in view of the large numbers of these patients referred to liver clinics, enables them to be discharged from regular follow up. The smaller number of patients with NASH with or without fibrosis however should be monitored for the development of advanced liver disease during regular follow up. Until alternative methods of distinguishing between fatty liver and more advanced disease are developed, without liver biopsy, clinicians will be committed to the indefinite follow up of the increasing number of patients under their care with suspected NAFLD.

Dr McNair's final argument against liver biopsy in these patients is that it does not influence treatment, which he states is limited to advising weight loss. There have been no randomised controlled trials of any treatment (including weight loss) providing evidence of histological benefit in patients with NASH. However, there have been a number of encouraging pilot studies reported thus far and randomised controlled trials based on these reports are now underway. It seems inconceivable therefore that within two or three years we will not have proven treatment of benefit for NASH and unless we are happy to treat all patients with NAFLD regardless of severity, then biopsy will be required to determine which patients require treatment. Dr McNair's argument that weight loss should be advised for all obese patients regardless of the severity of their liver disease is reasonable but it ignores the fact that, similar to the situation with heavy drinkers, obese individuals seem more likely to adhere to dietary advice if they know their obesity has seriously damaged their liver. It also assumes that the efforts made by clinicians in achieving weight loss in their patients will not be influenced by knowledge of the severity of any obesity associated end organ damage.

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Risk of gastric carcinoma in patients with atrophic gastritis and intestinal metaplasia

We read with interest the study of Whiting *et al* (*Gut* 2002;**50**:378–81) in which they reported an 11% risk of development of malignancy among patients with atrophic gastritis and intestinal metaplasia over a 10 year period. We agree with their conclusion that their findings should be further evaluated in larger studies, as confirmation of a high risk of malignancy would have important implications for clinical practice. We would however like to raise two issues.

Firstly, in Whiting's study, biopsies were taken only when there was macroscopic abnormality. These patients may therefore not be representative of the general population of dyspeptic patients with intestinal metaplasia.

We analysed 100 consecutive patients endoscoped for uncomplicated gastro-oesophageal reflux disease or functional dyspepsia for whom two biopsies were taken routinely from the antrum, body, and cardia, irrespective of macroscopic findings. The proportions of our patients with intestinal metaplasia, atrophic gastritis, both, or either were 17%, 27%, 6%, and 38%, respectively. Twenty of 27 patients with atrophy had mild changes: seven had moderate changes and none had severe atrophic gastritis. In four of 17 patients, intestinal metaplasia was widespread: 13 had focal changes. Thirty seven patients had *Helicobacter pylori* gastritis: 23 of these had concomitant atrophic gastritis and/or intestinal metaplasia. It seems unlikely that 4% (38%×11%) of our patients will develop gastric cancer over the next 10 years.

Our patients with atrophic gastritis and intestinal metaplasia are more representative of the general dyspeptic population and a different group from those studied by Whiting *et al*. Perhaps the high risk of malignancy they describe is associated with a combination of macroscopic abnormalities, the severity of the changes, the type of intestinal metaplasia, concomitant occurrence of intestinal metaplasia, atrophic gastritis, and *H pylori* infection rather than the histological findings per se. Long term follow up of a representative population of UK patients with uncomplicated dyspepsia is warranted. Meanwhile, we are concerned that their findings should not be uncritically extrapolated as the basis for surveillance recommendations for patients with uncomplicated dyspepsia and atrophic gastritis and/or intestinal metaplasia.

Secondly, what was the *H pylori* status of their patients with intestinal metaplasia and atrophic gastritis? In Uemura *et al*'s follow up study of 1526 Japanese patients over a mean period of 7.8 years,¹ gastric cancers developed in 2.9% of patients infected with *H pylori* but in none of the uninfected patients. Among patients with *H pylori* infection, those with severe gastric atrophy, intestinal metaplasia, and corpus predominant gastritis were at significantly higher risk. If the patients described by Whiting *et al* were *H pylori* positive, antibiotic treatment may be a more cost effective approach compared with endoscopic surveillance.³

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BOOK REVIEW



Somatostatin Analogs in Cancer Management

Edited by C Scarpignato. Nantes: Parma, 2001, US\$97.50, pp 198. ISBN 3 8055 7035 X

It may be common practice to publish book versions of journal supplements but this is the first such example to reach the desk of this reviewer (reprint of *Chemotherapy* 2001;**47**:supplement 2). In this age of instant electronic information retrieval the idea of producing such a hard copy version seems rather retrogressive, but for frequent referral it is still easier and quicker to reach for a book from the shelf than to suffer the vagaries of Internet access. But is this a book that needs to be at one's fingertips?

The book consists of a preface and introduction by the editor followed by a series of 10 invited reviews of different aspects of therapy with somatostatin analogues. These include overviews of the pharmacology and clinical applications of these compounds plus more specific chapters concerned with their use in the treatment of cancer of the breast, lung, prostate, gastrointestinal tract, pancreas, and liver, while the book ends with a quite comprehensive look into the future.

The book suffers from the shortcoming of nearly all textbooks in that it is not up to date. One would perhaps have expected better from a journal supplement but only a handful of the numerous references in this book date from later than 1998. That would not necessarily be a problem if the field had matured to the extent that recent developments would not significantly affect the take home message from the text, but that is not the case here where the molecular biology of the SRIF receptors has developed considerably in the last few years. The book also suffers from a high degree of repetition. If you did not know there were five receptor subtypes before reading this book, then you would be left in no doubt by the end since all 12 chapters would have told you so! Less facetiously the take home message from nearly all of the chapters is also the same—octreotide therapy should

work but it doesn't. The rationale for a cytotoxic/-tactic mechanism is clearly stated—indirectly through suppression of the GF/IGF-1 axis, inhibition of angiogenesis, reduction in T lymphocyte production, etc, and direct antiproliferative actions. However, with the exception of promising activity in the treatment of primary liver cancer, all of the proposed clinical indications fail to show any meaningful efficacy although many of the authors call for more controlled studies.

It is disappointing that despite featuring the use of targeted radiation on the front cover of the book, none of the chapters is devoted to this promising new modality although it merits several passing mentions.

This book represents a snapshot of the state of clinical application of somatostatin analogues in cancer in the late 1990s. There is undoubted utility in the palliation of the effects of hypersecretion of peptide hormones but no real indication of any useful cytotoxic activity in most cancers. Only time will tell if this turns out to be the end of the story.

S J Mather

NOTICES

Sir Francis Avery Jones BSG Research Award 2003

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2003 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 2002 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in March 2003. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2002.

Broad Medical Research Program—Inflammatory Bowel Disease Grants

Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli

and Edythe L Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US\$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no submission deadline), simple application, rapid (60 day) peer review, and funding. Criteria for funding includes new ideas or directions, scientific excellence, and originality. Early exploratory projects, scientists not currently working in IBD, and/or interdisciplinary efforts are encouraged. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

The national register of hepatitis C infections with a known date of acquisition.

The register steering group invite clinical and epidemiological researchers to submit proposals to access data held in the register. It is envisaged that a variety of studies might benefit from linkage with or access to the register, and proposals from all specialties and institutions are welcomed. Any researchers interested in applying for access to information held within the national register should contact the register co-ordinator (see below) for a list of available data and an application form. Study proposals should then be submitted to the register co-ordinator by **16 December 2002**.

Further information: Dr Helen Harris (Register Co-ordinator) or Ms Lisa Beck (Research Assistant), Immunisation Division, Communicable Diseases Surveillance Centre, Public Health Laboratory Service, 61 Colindale Avenue, London NW9 6EQ. Tel: +44 (0)20 8200 6868 ext 4496; fax: +44 (0)20 8200 7868; email: hharris@phls.nhs.uk or lbeck@phls.nhs.uk

17th International Workshop on Therapeutic Endoscopy

This will be held on 3–5 December 2002 in Hong Kong. Further information: Professor SC Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, Shatin, NT, Hong Kong. Tel: +852 2632 2233; fax: +852 2635 0075; email: info@hksde.org

Advances in the Inflammatory Bowel Diseases

This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imedex.com; website: www.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy

This course will take place on 16–17 December 2002 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis Rue des Cendriers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58.

The Future of Gastro-entero-hepato-pancreatology is bright

This Academic Farewell Symposium of Guido NJ Tytgat will be held on 12 December 2002 in Amsterdam, the Netherlands. Deadline for registration is 1 November 2002 (no registration fee) and registration should be done via email to: j.goedkop@amc.uva.nl.

Cancer of Oesophagus and Gastric Cardia: from Gene to Cure

This conference will be held on 13–15 December 2002 in Amsterdam, The Netherlands. Further information: European Cancer Centre, PO Box 9236, NL 1006 AE Amsterdam, The Netherlands. Tel: +31 (0)20 346 2547; fax: +31 (0)20 346 2525; email: ecc@ikca.nl

The Sheila Sherlock Memorial Symposium

Dame Sheila Sherlock, who died earlier this year, was responsible for creating hepatology at the Royal Free Hospital, London. This memorial symposium will take place on 26–28 January 2003 at the Royal Free Hospital, London, UK. Further information: Terri Dolan, Royal Free and University College Medical School, Royal Free Campus, Centre for Hepatology, Upper 3rd Floor, Rowland Hill Street, London NW3 3PF, UK. Tel: +44 (0)207 433 2851; email: t.dolan@rfc.ucl.ac.uk

3rd Chester International Inflammatory Bowel Disease Meeting

This meeting will be held on 10–11 February 2003 in Chester, UK. An international programme includes speakers from the USA, France, Italy, and the UK, and will cover clinical problems, pathogenesis, medical and surgical treatment. Registration details and programme from: Professor Jonathan Rhodes, Department of Medicine, University of Liverpool, Daulby Street, Liverpool L69 3GA, UK. Tel: +44 (0)151 706 3558; fax: +44 (0)151 706 5832; email: rhodesjm@liverpool.ac.uk