**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 lymphomas, it is necessary that we all speak the same language. To this end, many lymphomas, it is necessary that we all speak

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 neoplastic population” a “high grade” lymphoma. In response to my query 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 the “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 REAL classification explicitly states that marginal zone lymphomas should not be graded.1 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 lymphomas 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.

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

**References**


**Authors’ reply**

In our paper (Gut 2001;48:454–60), the recently proposed WHO classification of lymphoid neoplasms 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.

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.12 Based on these observations, we consider that high grade MALT lymphoma (MALT lymphoma) is a “high grade” 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.14 Many investigators still use the term “high grade MALT lymphoma”12,13,14,15 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.

**References**


mortality with oesophageal analysis.
showing better survival were included in the NBV group) only data from the treatment arm for at least one year. The few patients reported full between 1984 and 2001. Management in patients with known varices who had not for at least one year (group BV). For compari-
enced in survival between treatment arms and
varices has significantly decreased in the past few decades. Because of the limited follow up
reports showing that mortality from bleeding
immunostaining and identified them as IM-1, called Barrett CK7/CK20 pattern. IM-2 is char-
strong superficial CK20 stain. The authors report that both clinical and endoscopic find-
the origin and development of intestinal metaplasia at the gastro-oesophageal junction have been a matter for debate. There are find-
ments suggesting that intestinal metaplasia of the cardia has an immunophenotype similar to Barrett's oesophagus while others suggest that it is similar to that of the gastric mucosa. 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 endo-
strument and selected surgical specimens. 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 meta-
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 for-
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, 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

| 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)     | 31.4 (3.55)      |
| Range           | 14.7–71.1       | 9.6–65.2         |
| Year 3          | 46.0 (7.31)     | 46.0 (7.31)      |
| Range           |                |                 |
| Year 4          |                |                 |
| Range           |                |                 |

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 53.4 (0.90) years. Mortalities are shown in table 1.

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

There was no statistically significant differ-
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 bleed (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 differ-

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

<table>
<thead>
<tr>
<th>CK pattern</th>
<th>LS Barrett (n=17)</th>
<th>Cardia IM (n=15)</th>
<th>Corpus IM (n=14)</th>
<th>Antrum IM (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM-1</td>
<td>94%</td>
<td>7%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>IM-2</td>
<td>6%</td>
<td>80%</td>
<td>100%</td>
<td>91%</td>
</tr>
<tr>
<td>IM-3</td>
<td>0%</td>
<td>13%</td>
<td>0%</td>
<td>9%</td>
</tr>
</tbody>
</table>

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. Thus the significance of IM-2 and IM-3, as proposed by Mouzas et al, should be further clarified. In the small areas of intestinal metaplasia that are found in biopsy specimens from the gastro-esophageal 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-esophageal 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 clearly of gastric 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-esophageal junction. As the site of biopsy sampling may be critically important, we reviewed all gastro-esophageal junction biopsy specimens for histological evidence of the squamocolumnar junction. Among the 988 biopsy specimens corresponding to the 254 patients with an endoscopically normal gastro-esophageal junction included in our study, 582 (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-esophageal junction in 60 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-esophageal junction (266 biopsy specimens across the Z line, containing cardiac mucosa in 260 (97.7%) in association with fundic mucosa in 36/260 (13.5%) and containing only fundic mucosa in 6 (2.26%). These data, in line with those obtained in our autopsy series, support the concept that the gastric cardia is present as a constant structure. However, it must be remembered that some workers recently proposed the hypothesis that cardiac-type mucosa arises as a metaplastic phenomenon.

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References

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 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
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 under-estimate the number of colorectal polyps, especially in difficult cases. We believe that dye spray colonoscopy by an experienced endoscopist and careful examination of colec- tomy 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.

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

FAP, familial adenomatous polyposis.

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

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. 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 polyps and the APC gene mutation were compatible with FAP of the attenuated form.1

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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References


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 surveil- lance 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 investi- gated 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. 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 proto- col 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

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 patholo- gists and it has been recommended to diagnose “atrophy” only when appropriate gastric glands are replaced by intestinal epithelium or by fibrosis.1 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 corpus mucosa are also important. In fact, it has been demonstrated that corpus predominant gas- tritis related hypoachlorhydria is a key factor in the multistep carcinogenesis cascade.2

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,3 even if the possible effect of H pylori cure in premalignant conditions is still a matter of discussion.

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 meta- plasia in the gastric body or in those who were H pylori positive, but these data were not pro- provided.

In conclusion, while we agree that surveil- lance 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 gastrointestinal malignancies.

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References

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 disorders in coeliac disease 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) published 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”, artifically 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 multi-variable 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 (2 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 confirmatory 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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References

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 Lonedi in his commentary on our article, ‘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 conducted between 1975 and 1985 was the only selective 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 whose gluten withdrawal, recorded while, neither diet compliance (it is well known that many teenagers are non-compliant!) nor intestinal mucosal 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 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 both studies” 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 Lonedi.’

The “strong” age at diagnosis variable can be biased by screening procedures and medical awareness directed to both coeliac and autoimmune (AI) diseases. 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 point 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.

In this study, 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 (±18) years compared with 23% in Ventura et al’s study in patients aged 15 years old (±6.3), 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.
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 aetiology, diagnostic criteria, 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 so why 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 (AST) more than twice the upper normal limit, “moderate” central obesity, non-insulin-dependent diabetes, hypertension, and/or 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 are known to 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 give unexpected findings and the results may allow more accurate prognostic information to be given to the patient.

Sherwood and colleagues 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, only half were thought to require further investigation, approximately one third of whom had normal results on repeat testing. Following investigations 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), serology, total cholesterol, triglycerides, markers of iron overload, primary biliary cirrhosis, α1 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 disease 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. The presence of cirrhosis will affect patient management but, as Day points out, 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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References

of the findings on liver biopsy.

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 colleagues along with our own study 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 an excellent 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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References


Risk of gastric carcinoma in patients with atrrophic 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 atrrophic 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, atrrophic 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 occurred atrophic gastritis and/or intestinal metaplasia. Thirty seven patients had Helicobacter pylori gastritis: 23 of these had concomitant atrophic gastritis and/or intestinal metaplasia. It seems unlikely that 4% (38%) of our patients will develop gastric cancer over the next 10 years.

Our patients with atrrophic 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, atrrophic 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 atrrophic gastritis and/or intestinal metaplasia.

Secondly, what was the H pylori status of their patients with intestinal metaplasia and atrrophic gastritis? In Uemura et al’s follow up study of 1526 Japanese patients over a mean period of 7.8 years, gastric cancers developed in 2.9% of patients infected with H pylori but 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.

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Somatostatin Analogues in Cancer Management


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. The book includes a regular feature entitled ‘Chemotherapy’ (Gut 2002;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 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

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work but it doesn't. The rationale for a cytotoxic-taxic 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 of a detailed proposal) is required (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 Administrator), Immunisation Division, Communicable Diseases Surveillance Centre, Public Health Laboratory Service, 61 Colindale Avenue, London NW9 6EQ. Tel: +44 (0)20 8200 6666 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, Imdex, 70 Technology Drive, Alpharetta, GA 30005-3969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imdex.com; website: www.imdex.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-pancreateology 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 2831; 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: rhodesj@liverpool.ac.uk