LETTERS TO THE EDITOR

Grading system for inflammation in ulcerative colitis

EDITOR,—Geboes *et al* described a grading system for inflammation in ulcerative colitis and carried out rigorous assessment of the reproducibility of this system (*Gut* 2000;47:404-9). This is a very useful study which fills a void in the histopathology assessment of ulcerative colitis. However, now that this system has been described, its use in clinical practice and clinical trials needs to be considered.

Many of the features that Geboes *et al* have used in their grading system are described as continuous spectra—for example, chronic inflammation assessed from no increase through to marked increase—but are divided into discrete groups (for example, mild, moderate, marked). This means that these features are ordinal categorical variables rather than continuous real numbers—that is, they have a numerically labelled order but the distance between adjacent numbers will not be the same through the whole range and there are no non-integer values.¹ The consequences of this are that these grades cannot be used in processes which require continuous variables, such as linear regression.² The authors already seem to have made this mistake themselves as they give mean grades of the system in table 2 (to two decimal places), when they should have given frequency distribution histograms or possibly median grades with centiles as an indicator of spread. They do not state which method they used to measure the correlation between location of neutrophils in the epithelium and occurrence of crypt destruction, erosions, and ulcerations (table 4 and last paragraph of results section).

The nature of ulcerative colitis as a chronic relapsing condition means that many studies and trials require a measure of inflammatory activity and need to relate this to other measured parameters. It is likely that this new grading system will be used in clinical trials of new treatment regimens. The ordinal categorical properties of the new grading system means that measures such as mean grade should not be used in comparing groups of patients before and after treatment or between groups of patients receiving different treatments.

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Reply

EDITOR,—We appreciate the comments of Dr Cross on our paper in which we presented the results of a reproducibility study of a grading system for inflammation in ulcerative colitis. We agree that certain features used in the

grading system in reality present as continuous spectra. Therefore, the scoring system is composed of major grades and subgrades. The features which represent the major grades such as architecture and infiltration of round cells are clearly different from each other. The continuous spectrum exists within the grades, especially for architectural changes and chronic inflammation. Major grades are divided into different subgroups (for example, mild, moderate or diffuse) and these are indeed ordinal categorical variables. The situation is even more complex. Indeed, the inflammatory cell population in the lamina propria is heterogeneous. It includes T and B lymphocytes, plasma cells, and CD68⁺ monocytes. These cells can synthesise cytokines or immunoglobulins, or express markers such as LFA-1 or ligand-receptor pairs such as CD40-CD40L which might be important for disease activity. In the past it has been shown for instance that there is a correlation between disease activity and immunoglobulin containing cells.¹ Hence changes in "chronic inflammation" do not have only a continuous spectrum. There are changes in subtypes of cells, and these changes show a continuous spectrum. Analysis of routinely haematoxylin and eosin stained sections is therefore obviously limited. The aim of our study was to construct and evaluate a scoring system which can be applied routinely. In this system, the distinction between the major grades (for example, structural change, chronic inflammatory infiltrate, infiltration of neutrophils in the epithelium, crypt destruction, and erosion or ulceration) is much more important than the subgrades. The differences between these major grades are clearly defined and do not present as a continuous spectrum. A change from one grade to another is a major difference, which can indicate an important effect, while changes within a grade from mild to moderate are far less important. Furthermore, the distinction between active disease (neutrophils and epithelial damage) and inactive disease is clearly defined. For evaluation of neutrophils in the epithelium, the number of crypts involved was counted.

The results of the reproducibility study presented in table 2 as mean grades were meant to show an example of interobserver agreement. Frequency distribution histograms of the same data are available but were not included, perhaps wrongly, because we had to limit the data which were submitted for publication to keep the paper within a reasonable length. The score allows a good comparison for each individual patient as well as a comparison for the major grades and numbers of patients within each grade. The latter allows comparisons between patient groups. The scoring system is under prospective evaluation in clinical trials and has so far been easy to use for routine assessment of microscopic inflammation. The results will be published in due course.

We realise that the distinction between different groups within one grade is not rigorously correct but we still feel that it can be useful, especially as we decided to use the worst aspect for the grading, rather than an average aspect. The correlation between location of neutrophils in the epithelium and occurrence of crypt destruction, erosions, and ulcerations was studied using Spearman's correlation coefficients.

In general, we agree with Dr Cross that a correct scoring system is needed. On the other hand, such a scoring system should be

simple and easy to use. We have tried to find a balance between the different needs and have shown that such a system can be applied with fair interobserver agreement.

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Insulin and gall stones

EDITOR,—In showing for the first time that raised serum insulin is a risk factor for incident gall stones, independent of body mass index, Misciagna *et al* (*Gut* 2000;47:144-7) have made an important contribution. However, they do not seem to realise that we had similar findings in the East Bristol Gallstone Study (population based like theirs)—namely, that raised plasma insulin is a risk factor for prevalent gall stones, at least in men.¹ In our study, another significant factor was abdominal fatness or central obesity, but not body mass index (as is usually the case in men), and abdominal fatness probably explained the hyperinsulinaemia as the association of insulin with gall stones disappeared when we controlled for waist-hip ratio. Abdominal fatness is a well known determinant of fasting plasma insulin and it is a pity that Misciagna *et al* did not include any measure of it in their study.

Should Misciagna *et al* continue this line of enquiry, they will be well advised to measure the insulin response to eating because in our experience, postprandial as well as fasting levels of insulin are raised in men with gall stones.¹ I fully agree with Misciagna *et al*'s conclusion that "hyperinsulinaemia may play an important role in the aetiology of gall stones". I also suggest that future studies of gall stone aetiology should include measures of insulin sensitivity and of its determinants. One such determinant is physical fitness² and this may be relevant because, in our study, there was a hint that loss of muscle bulk may be associated with gall stones in men. Men with gall stones had not gained weight during adult life more than controls, despite having more abdominal fat, suggesting they had lost more lean body mass.¹

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- 2 Houmard JA, Wheeler WS, McCammon MR, *et al.* Effects of fitness level and the regional distribution of fat on carbohydrate metabolism and plasma lipids in middle- to older-aged men. *Metabolism* 1991;40:714–19.

Reply

EDITOR,—We thank Drs Heaton and Emmett for their interest in our paper (*Gut* 2000;47:144–7) and the insightful comments. We regret not having cited their previous research findings on the relationship between plasma insulin and prevalent gall stones.¹ We agree that waist to hip ratio may be an important variable to consider. However, waist to hip ratio and insulin are intimately related in the pathophysiological pathways linking insulin resistance to gall stone formation, therefore the interpretation of results from analytical models, including both of these variables, may be problematic. In addition, we concur with the potential importance of physical fitness, and would like to add that physical activity may also play a role in the aetiology of gall stones. Our conclusion is based on the findings from a previous paper by our group showing a strong association between physical activity and incident gall stones in a population based case control study.²

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Heparin as an anti-inflammatory agent: it's no GAG to forget about chemokines

EDITOR,—We approached with enthusiasm the report by Salas and colleagues (*Gut* 2000;47:88–96) showing that heparin prevented tumour necrosis factor α induced leucocyte rolling, adhesion, and migration in vivo, as demonstrated using intravital microscopy. The novelty and potential importance of the report were emphasised by the appearance of an accompanying commentary by Perretti and Page (*Gut* 2000;47:14–15). Our enthusiasm was tempered, however, by the authors' selective invocation of potential explanations for heparin as an anti-inflammatory agent. While an effect of heparin on the neutrophil integrin adhesion molecule CD11b was described in elegant experiments, heparin almost certainly exerts its anti-inflammatory effects through a range of activities beyond an adhesion molecule target. One of these targets is the superfamily of cytokines known as chemokines, over 40 of which have now been identified.¹

Chemokines are small, basic, chemotactic cytokines that mediate leucocyte recruitment to sites of inflammation and immune responses.^{2,3} In addition, it is now clear that

they are crucial to routine immune surveillance and homeostasis.⁴ They have a capacity to bind selectively to a range of glycosaminoglycans, or GAGs, including heparin, in tissues and on the surface of both endothelial cells and leucocytes. This interaction heightens migration along a fixed gradient, or so-called haptotaxis,⁵ and favours receptor binding.⁶ There is strong evidence that soluble GAGs, including heparin, prevent chemokines binding to their receptors, thus abrogating their chemotactic potential.⁷

Neither Salas and colleagues nor Perretti and Page chose to mention an anti-chemokine mechanism for the anti-leucocyte migration activity of heparin. We ignore chemokines at our peril though, as their sheer number and abundance, and the intensity of the effort being directed at discovering pharmacological inhibitors of their function, highlight their critical role in inflammation.

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Management of variceal haemorrhage in cirrhotic patients

EDITOR,—We have serious concerns about several of the recent UK guidelines for the management of variceal haemorrhage in cirrhotic patients (*Gut* 2000;46(suppl 3 and 4):iii1–iii115), particularly those that contradict current published evidence. We highlight below the ones we feel are the most important.

In the management of acute variceal bleeding, variceal ligation is not the method of first choice which was given an AI recommendation. Meta-analysis of all trials of acute bleeding of banding versus injection sclerotherapy have shown no statistically significant difference between the two treatments for either control of bleeding or survival (data derived from 12 studies with 419 patients), with no statistical heterogeneity.¹

The implication of recommending ligation for acute bleeding is that double intubation would be necessary in a patient who is actively bleeding so as to attach the ligation device after the initial diagnostic endoscopy. Although there is no evidence, this would create more risk to the patient; it is common

sense that a single intubation would be preferable and would take less time. At best the recommendation should be that either endoscopic technique could be used as first choice, dependent on operator expertise and facilities.

Secondly, there is evidence from randomised studies of vasoactive drug therapy combined with endoscopic techniques that combination therapy is superior in terms of control of bleeding. This is based on five randomised studies with 610 patients (pooled odds ratio 0.42, 95% confidence interval 0.29–0.6).¹ Publication bias assessment has shown that 29 null or negative studies would be needed to render the results non-significant, and thus this effect is fairly robust. Moreover, in several of these studies vasoactive drugs were given before diagnostic endoscopy, demonstrating their utility during the period of resuscitation before endoscopy could be safely performed, which in practice may be several hours after admission. This goes against the recommendation that drugs can be used if endoscopy is not available. Drugs should be used first followed by therapeutic endoscopy.

As regards the prevention of rebleeding from sources due to portal hypertension, the treatment of first choice, unless there are contraindications, is either non-selective β blockers as they are equivalent to sclerotherapy,¹ or band ligation. No fully published randomised studies are available with regard to β blockers versus banding. If banding is not available, β blockers should be used, not sclerotherapy, as recommended. If there are contraindications or intolerance to β blockers, banding should be used. One can argue cogently that as non-selective β blockers are cheap and do not involve repeated endoscopy sessions, they always should be considered the treatment of first choice.

The recommendation of measuring hepatic venous pressure gradient (HVPG) in patients given β blockers cannot be one for current practice. Only two Spanish groups have suggested this, and it is unclear when a repeat measurement should be performed. Moreover, both a 20% reduction from baseline HVPG or an absolute reduction to less than 12 mm Hg are "protective" from rebleeding, so both end points, and not just the absolute reduction, need to be mentioned if this management strategy is used. In any case the randomised studies versus sclerotherapy used non-selective β blockers empirically to the maximum tolerated by patients so that use of drugs without pressure measurement was effective. Lastly, if the recommendation of using drugs with re-measurement of pressure is taken to its logical conclusion, all patients should be tried on drugs first, as those who respond have far less rebleeding (10% or less) than patients who receive banding, and secondly, a recommendation of what to do next would need to be made for those who do not reduce their portal pressure (for which as yet there is no evidence).

Lastly, two meta-analyses comparing TIPS with endoscopic techniques showed that TIPS did not improve survival.^{2,3} The increased encephalopathy, greatly increased cost, as well as poor availability of TIPS treatment does not make it a first choice treatment for rebleeding, even in centres with expertise such as the authors' own, as stated in the guidelines. Thus the AI recommendation grading is particularly inappropriate.

With respect to primary prevention of portal hypertensive bleeding in cirrhotics, the