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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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

recommendation that nitrates should be used if neither β blockers nor banding are available or contraindicated is potentially dangerous. A long term randomised study has shown that at least in elderly patients, nitrates on their own decrease survival.¹ Thus to err on the side of caution, nitrates cannot be recommended as a substitutive therapy.

Finally, the guidelines should have included some issues of general management—for example, resuscitation with fluids, early assessment of portal vein patency, and presence of hepatocellular carcinoma—and an AI recommendation for the use of prophylactic antibiotics in acute bleeding based on the meta-analysis the authors quoted.⁵ A corrected and improved update of these guidelines is needed soon.

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Reply

EDITOR,—We thank Dr Burroughs and Dr Patch for their interest and helpful comments on the UK guidelines in the management of variceal bleeding. A number of the points raised by them reflects the fact that it is not always possible to directly translate the evidence that is gleaned from clinical trials into clinical practice because of the subjectivity in the definition of evidence based medicine. There is a lot of argument in the literature about what constitutes research evidence. Indeed, there is ongoing debate whether the results of a good randomised controlled trial are more reliable than a meta-analysis on the same subject because the latter often suffers from problems introduced by heterogeneity between studies.^{1,2}

For the preparation of the present “guidelines”, about 300 papers were reviewed and 208 have been referred to in the paper. It is clear that the vast majority of these studies were not adequately powered to detect differences in mortality and a number of points that have been raised by Dr Burroughs and Dr Patch represent alternative interpretation of the available data which are not necessarily at variance with the “guidelines”.

Before discussing the specific points raised by them, it is important to point out that:

- Although the guidelines were written by us, they have undergone several revisions based on peer review organised by the

British Society of Gastroenterology (BSG), Liver Section. This review process we believe was extensive and largely anonymous. The guidelines therefore represent the views of the BSG.

- The guidelines were first commissioned in 1996 but finally accepted for publication following several alterations in mid-1998. Some of the more important data were added into the text (the antibiotic prophylaxis section) during the proof stage.

With respect to the specific comments:

(a) We agree with Dr Burroughs and Dr Patch that studies have not shown any significant differences between band ligation and sclerotherapy in their ability to control bleeding. Also, most patients who have had a variceal bleed and are undergoing endoscopy are not bleeding actively. It is therefore relatively easy to band in these situations and a double intubation using the new multi-band ligation devices is not necessarily a problem. Studies have also shown that complications from endoscopic therapy in the form of oesophageal ulcers, mediastinitis, and pneumonia are significantly less in the group treated with band ligation compared with sclerotherapy. This is associated with reduced mortality in patients treated with band ligation. It stands to reason therefore that band ligation should be used where possible as there is no significant difference between treatments in their ability to control bleeding but the rate of complications has been shown to be significantly less in the band ligation group.^{3–6}

(b) Interpretation of data regarding the combination of vasoactive drugs with endoscopic therapy in the setting of acute bleeding is fraught with difficulties and there is no clear evidence that the combination reduces mortality. This is despite a large number of trials in this area. The meta-analysis that Burroughs and Patch (published in 1999) refer to as a justification for the combination treatment shows no differences in survival between groups.⁷ The role of vasoactive drugs in the management of variceal bleeding is an area of intense research by a number of groups and data are needed before the combination treatment can be recommended in routine clinical practice.

(c) With respect to secondary prophylaxis of variceal haemorrhage, the literature suggests that various treatments such as sclerotherapy, β blockers, or a combination of these are similar in the long term (reviewed by D'Amico and colleagues⁸). Most patients that we treat in the UK with variceal bleeding have underlying alcoholic liver disease and who have a questionable compliance. The recommendation is that if only a β blocker is used we should ensure that this is having some effect on the most important parameter predictive of rebleeding, a portal pressure gradient <12 mm Hg (about 30% of patients in different studies show inadequate portal pressure response to β blocker therapy). It has been shown in a prospective study that in patients being treated with β blockers, none with a hepatic venous pressure gradient <12 mm Hg bled and only 8% of those whose hepatic venous pressure gradient fell by more than 20% on therapy bled during follow up.⁹ However, if portal pressure studies are included in patients being treated with β blockers, this is likely to increase both the cost and invasiveness. We do agree that we should add to the guidelines that a reduction in portal pressure gradient by 20% or more from baseline is acceptable.

(d) The guidelines clearly state what Dr Burroughs and Dr Patch suggest in their letter: “TIPSS is more effective than endoscopic treatment in reducing variceal rebleeding but does not improve survival and is associated with more encephalopathy”. Three studies have shown that TIPSS is as cost effective as endoscopic treatment.^{10–12} The only study that suggests that TIPSS is more expensive is an Italian study in which TIPSS was not strictly being used for secondary prophylaxis with patients being randomised for as long as six months after their initial variceal bleed.¹³ Studies that have compared TIPSS with band ligation have not shown any significant differences in encephalopathy between groups.^{10,14} This has, however, not been borne out in a meta-analysis.¹⁵ But it is clear from individual trials and also from the meta-analysis that TIPSS significantly reduces the rate of rebleeding.

(e) The recommendation grade for the use of isosorbide-5-mononitrate (ISMN) in case of failure of propranolol or band ligation is grade B1 and is based on the equivalence study of ISMN and propranolol by Angelico and colleagues.¹⁶ The paper that Dr Burroughs and Dr Patch refer to is a post hoc analysis of data from a study that was first reported in 1993.¹⁷ A preliminary report of another study has not confirmed these findings¹⁸ and it is clear that more data are needed before nitrates can be suggested as being dangerous in the primary prophylaxis of variceal bleeding.

(f) Our brief was to develop guidelines about the management of variceal bleeding and not about the detailed intensive care management. We have however included some pointers in the guidelines which we thought were likely to be useful. We accept that the use of prophylactic antibiotics should be a grade 1A recommendation. This section on the use of antibiotics following a variceal bleed was added during the proof stage following the availability of the meta-analysis by Bernard *et al* in 1999.¹⁹

We do agree with Dr Burroughs and Dr Patch that the treatment options in portal hypertension are continuously evolving and with the emergence of new data, “guidelines” should be revised to incorporate the advances that have occurred in that time.

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Long term follow up of interferon responder children with chronic hepatitis B

EDITOR,—We read Bortolotti *et al*'s article (*Gut* 2000;46:715-18) reporting the long term effect of interferon (IFN) alpha in children with chronic hepatitis B (HBV). Briefly, a total of 107 children with chronic HBV who received IFN alpha for three or six months in two clinical trials were followed for a mean period of 69 months. In the first trial 19 and 20 cases received IFN alpha at a dose of 3 and 7.5 MU/m² three times a week for six months, respectively. In the second trial 34 cases received lymphoblastoid IFN at a dose of 5 MU/m² for 12 weeks and 30 cases received IFN at the same dose but preceded by a four week course of prednisolone. Response to treatment was defined as loss of hepatitis B e antigen (HBeAg) within 12 months after stopping treatment. A control group of 59 patients was also followed for a mean period

Table 1 Number (%) of patients who cleared HBeAg at different times in the four treatment groups

Time	Group 1 (n=8)	Group 2 (n=34)	Group 3 (n=5)	Group 4 (n=12)	Total (n=59)
End of treatment	6 (75%)	23 (67.6%)	3 (60%)	6 (50%)	38 (64.5%)
12 months after stopping treatment	6 (75%)	32 (94.1%)	5 (100%)	12 (100%)	17 (28.8%)
End of follow up	8 (100%)	34 (100%)	5 (100%)	12 (100%)	59 (100%)

Interferon alpha dosage and duration: group 1, 10 MU/m² three times a week for six months; group 2, 5 MU/m² three times a week for six months; group 3, 5 MU/m² three times a week for 12 months; group 4 (non-responders to previous interferon alpha treatment), 10 MU/m² three times a week for six months.

of 46 months without any therapy. Sixteen (15%) treated children responded during therapy and 18 (17%) during post-treatment follow up; 31 (29%) non-responders lost HBeAg during subsequent years. The cumulative HBeAg clearance rates at five years were similar between treated patients (60%) and controls (65%). Loss of hepatitis B surface antigen (HBsAg) occurred in only four patients who responded during treatment.

We also wish to report on the long term follow up of 59 IFN responder children with chronic HBV (table 1).¹⁻³ At the beginning of IFN therapy, all children (44 males; 74.6%) had abnormal or fluctuating transaminases for at least six months and were positive for HBV DNA. Mean age of the patients at diagnosis of chronic HBV was 6.8 (3.4) years (range 1-15). They were followed for a mean period of 19.9 (21.5) months (range 6-100) before treatment. Liver biopsy was performed on 29 patients; 15 (51.7%) had mild, 12 (41.4%) moderate, and two (6.9%) severe hepatitis. Forty three (84.3%) of 51 patients had at least one family member with positive HBV serology. Eight patients (group 1) had received IFN alpha at a dose of 10 MU/m² three times a week for six months,¹ 34 (group 2) at a dose of 5 MU/m² three times a week for six months² or 12 months (five patients, group 3). Twelve patients (group 4) who were unresponsive to IFN therapy at a dose of 5 MU/m² received IFN alpha again at a dose of 10 MU/m² three times a week for six months.³ Response to treatment was defined as loss of HBeAg during the treatment period or within 12 months after stopping treatment. All patients were followed for a mean period of 35.3 (10.8) months (range 18-62) after starting treatment. Thirty eight (64.5%) patients cleared HBeAg at the end of IFN therapy and 17 (28.8%) within 12 months after stopping treatment. Four (6.7%) patients were late responders (HBeAg clearance was observed between 21 and 30 months after stopping therapy). The mean period of HBeAg clearance was 8.2 (7.0) months. Within the follow up period, antibody to hepatitis B surface antigen (anti-HBs) occurred in seven (18.4%) patients who responded during therapy and all but one lost HBsAg. After HBeAg clearance, anti-HBe seroconversion and loss of HBV DNA was observed in all patients. Alanine aminotransferase values normalised in 98.3% of patients. None had biochemical or serological relapse within the follow up period.

The majority of our patients cleared HBV DNA and HBeAg during therapy whereas only 15% of patients in the study of Bortolotti *et al* responded during therapy. They followed patients for an average of 69 months and observed that all IFN responders remained HBeAg and HBV DNA negative. Although our observation period was shorter than theirs, we also observed that all responders had sustained results at the end of follow up. Similar to Bortolotti *et al*'s results, all HBsAg cleared patients were early responders to IFN

therapy in our group. In conclusion, response to IFN alpha in children with chronic hepatitis B is permanent. It is necessary to follow these patients for longer periods to see the long term effects of IFN alpha therapy, such as prevention of cirrhosis and/or hepatocellular carcinoma.

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Renal sodium handling in preascitic cirrhosis

EDITOR,—We read with interest the commentary by Clària and Rodés (*Gut* 1999;45:639) on our paper published in *Gut* which re-examined the mechanisms of renal sodium retention in patients with preascitic cirrhosis.¹ In summary, in our patients we observed indirect evidence of expanded central vascular fluid volume compared with healthy controls and thought this physiopathological alteration was due to slightly reduced values of glomerular filtration rate (measured as creatinine clearance) and, mainly, to increased distal tubular retention of sodium when expressed as a fraction of the filtered sodium load that is reabsorbed by the distal nephron (26.9 (6.7)% v 12.5 (3.4)%, respectively; $p < 0.05$).¹

Clària and Rodés advanced two criticisms and affirmed that our results, obtained by means of the lithium clearance and fractional excretion technique, may be influenced by two fundamental flaws. Firstly, the reliability of lithium clearance as a marker of distal fluid delivery in clinical conditions characterised by low fractional sodium excretion (below 0.40%) has not been proved due to possible lithium reabsorption in the distal nephron.² Secondly, in Clària and Rodés's opinion, our observation of more avid fractional sodium reabsorption by the distal nephron in compensated cirrhosis merely reflects diminished delivery of fluid and sodium to the distal segments (due to reduced glomerular filtration) rather than increased distal tubular sodium reabsorption.

With reference to the first methodological remark, to our knowledge the value of fractional sodium excretion (FENa) below which lithium reabsorption beyond the proximal tubule occurs is 0.02% and not 0.4%.^{3,4} Obviously, our non-azotaemic preascitic cirrhotics displayed values of FENa well above this threshold (0.76 (0.39)%).¹

Concerning the second remark, although our patients displayed slightly lower values of creatinine clearance (CCr) with respect to controls, the calculated deliveries of fluid and sodium to the distal nephron were not lower but somewhat higher, even if not significantly, than in healthy subjects (30.7 (9.3) v 27.5 (6.7) ml/min and 4.25 (1.30) v 3.9 (1.0) mEq/min, respectively; all $p > 0.05$).¹ In effect, not surprisingly, we observed no correlation between values of CCr and distal delivery of fluid or sodium.¹ Furthermore, because of the inverse correlation in the cirrhotic group between levels of plasma active renin and lithium clearance, we reaffirm a compensatory role for the proximal renal tubule as it seems capable of delivering more fluid and sodium to the loop of Henle during a progressive increase in circulating fluid volume, at least at this stage of disease.¹

In conclusion, we agree with Clària and Rodés that some uncertainty may be introduced in studies assessing renal function in cirrhosis by measurement of glomerular filtration rate using creatinine clearance. However, we consider that our results on inappropriate avidity of sodium reabsorption by the distal nephron are relevant in explaining the already demonstrated increase in central fluid volume in patients with preascitic cirrhosis.⁵

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- 1 Sansoè G, Ferrari A, Baraldi E, *et al*. Renal distal tubular handling of sodium in central fluid volume homeostasis in preascitic cirrhosis. *Gut* 1999;45:750–5.
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Reply

EDITOR,—In their letter, Sansoè and Ferrari make some excellent points on our accompanying commentary (*Gut* 1999;45:639) to their paper published in (*Gut* 1999;45:750–5). In that paper, Sansoè *et al* investigated the status of central blood volume and examined the distribution of sodium reabsorption along the segments of the renal tubule in a group of 12 preascitic cirrhotic patients. Whereas the results on central fluid volume were quite conclusive, the findings on renal function merit some discussion (*Gut* 1999;45:639). As precisely pointed out by Sansoè and Ferrari in their letter, the contention was mainly methodological and was related to the use of

lithium and creatinine clearances for determination of distal sodium reabsorption and glomerular filtration rate, respectively.

Lithium clearance is a useful marker of proximal tubule sodium handling because in theory this ion is reabsorbed in proportion to sodium and water along the entire proximal tubule.¹ However, the validity of this method is not widely recognised. In this regard, there is compelling evidence that lithium is actively reabsorbed along the distal tubule in conditions characterised by low fractional sodium excretion.² In healthy subjects, the estimated limit of fractional sodium excretion below which this problem arises has been established as 0.02%.³ Conversely, comprehensive studies of micropuncture have revealed that this value may vary from 0.4% to 0.65% in sodium depleted states.^{4,5} Finally, a value of fractional sodium excretion of 1% has been proposed as a safer limit by Koomans and colleagues.⁶ Thus, inasmuch as the value of fractional sodium excretion below which lithium clearance is disqualified as an index of proximal sodium delivery remains unresolved in cirrhosis, data derived from this method in cirrhotic patients should be interpreted with caution.

We should also point out that preascitic cirrhotic patients included in Sansoè *et al*'s study (*Gut* 1999;45:750–5) had significantly lower values than controls for glomerular filtration rate, as determined by creatinine clearance. These findings are not consistent with those previously reported in compensated cirrhotics using more sensitive clearance techniques such as inulin clearance.⁷

In summary, it is gratifying to see that Sansoè and Ferrari agree that a certain amount of uncertainty may be introduced in studies dealing with renal function by using creatinine and lithium clearances. We believe that their paper will undoubtedly foster new studies investigating the central fluid volume status and renal tubular avidity for sodium in preascitic cirrhotic patients.

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BOOK REVIEWS

Comprehensive Clinical Hepatology.

Edited by JG O'Grady, JR Lake, PD Howdell (illustrated; £129.00). UK: Harcourt Publishers, 2000. ISBN 0-7234-3106-X.

The rapid and exciting developments in hepatology in recent years make an innovative and comprehensive textbook of clinical hepatology very welcome. The editors, who are themselves international authorities in the field, have assembled an impressive array of multinational hepatological talent to compile their comprehensive textbook of clinical hepatology. It is a pleasure to read a textbook where each of the chapters is written by an authority in the field. One problem of such multiauthor books can be the often jarring changes in style between different contributors, but the editors of this book are to be congratulated in assimilating a diverse group of writers and editing their work into a uniform and very readable style. The other aspect of this book, which impresses you immediately, is the clarity of the presentation, particularly the figures. The book is beautifully laid out and the figures are superb. If the publishers made these figures available on a CD-ROM, I am sure that all of us who lecture on liver disease would snap them up immediately. The surgical chapters are particularly impressive, not only for the quality of the figures and the straightforward explanation of the techniques, but also because they have been included in a textbook of hepatology. This is evidence of the multidisciplinary approach, which is such an important part of treating patients with liver disease. Given the interest of the editors it is not surprising that liver transplantation is given the prominence it deserves in a textbook of hepatology and the subject is covered comprehensively from surgical techniques and patient selection through to the excellent chapter from Geoff McCaughan on immunology and immunosuppression. Other highlights include the superb chapter by Fan and Steer on cell biology, where again the quality of the illustrations makes it a pleasure as well as an education to read, and a welcome chapter on the liver in the critically ill, a common but often neglected clinical problem.

So are there any criticisms? I have a few complaints about areas that in my opinion have been neglected. The chapters are organised by individual diseases, which means that some of the more general processes are not covered in full. For instance, it would have added to the book to have a chapter on fibrogenesis and the development of cirrhosis; two other areas that probably warrant a chapter of their own are radiology, particularly with the increasing capabilities of interventional radiologists, and the role and interpretation of liver biopsy. As far as clinical areas are concerned, I could find no mention of liver disease in bone marrow transplantation, a difficult area which would benefit from being covered in a book such as this. A minor quibble is the indexing which I would revise for the next addition. There are several omissions; for example, benign intrahepatic cholestasis and veno-occlusive disease are both discussed in the text but not listed in the

index and I personally do not like the idea of paginating in sections and chapters. With a book of this length it is surely easier to simply number the pages. However, these are minor complaints and on the whole I would recommend this book to anyone interested in liver disease and particularly to trainees in gastroenterology, hepatology, or hepatobiliary surgery who will come back to this book again and again.

D H ADAMS

Atlas of Gastroenterology, 2nd edn. Edited by T Yamada, DH Alpers, L Laine, *et al* (Pp 928; illustrated; £130.00). USA: Lipincott Williams and Wilkins, 1999. 0-397-58767-8.

"A picture is worth a thousand words" is as applicable to the teaching of gastroenterology as in any other context now that gastroenterology has become a visual science. Any atlas must stand or fall on the quality of the photographs and here the reader will not be disappointed as the vast majority are of excellent clarity and content. The second edition of this *Atlas of Gastroenterology* provides the most comprehensive visual images in gastroenterology this reviewer has seen, covering the broad spectrum of gastroenterology—histology, endoscopic images, CT scans, radionuclide imaging, and magnetic resonance imaging, including MR cholangiopancreatography. However, there are no "virtual endoscopy" images, which is a surprise and disappointment.

The atlas has a user friendly format setting pictures in their clinical context making perfect sense and easy access. There is a series of chapters entitled "Approaches to common gastrointestinal problems" beginning with a brief review of the clinical problem followed by a range of images used in establishing diagnosis, thus putting the image in context with the clinical findings at the appropriate point in the management pathway. There are also chapters on particular gastrointestinal diseases and a series of chapters illustrating diagnostic and therapeutic techniques, all written and compiled by acknowledged experts in their field. Reference lists are suitably brief and up to date.

The atlas seeks to provide more than a picture book of gastroenterology but perhaps goes rather too far by providing information that would normally be within a textbook of gastroenterology. For example, there is a chapter entitled "Advice to travellers" that gives information about required vaccinations in various parts of the world and drug treatment for traveller's diarrhoea. There are also several chapters with extensive clinical information that is more than just an accompaniment to the images. In one chapter, there is a long list of drugs likely to induce liver disease—appropriate for a textbook but not for an atlas, particularly when this atlas is designed for use with its partner the *Textbook of Gastroenterology* by the same editors.

This atlas provides the most up to date high quality illustrative review of gastroenterology and could perhaps only be improved by the addition of a slide or CD version. Access to the images via the Internet will probably be the next step but I for one would miss the pleasure of leafing through a book.

S CAIRNS

Endoscopic Gastric Surgery. Edited by E Hanisch, M Kitajima, T Wehrmann, *et al* (Pp 134; illustrated; £51.50/DM 149.00). Germany: Springer Verlag, 2000. ISBN 3540653333.

This is a small textbook which looks at specific aspects of gastric surgery from a laparoscopic approach. The overall format is attractive in that a chapter on physiology precedes the section on laparoscopic surgery. It does, however, in view of the rather concise nature, fall between two stools in that it is a specialist book and therefore does not necessarily appeal to the general trainee, but it is too short and the referencing is too limited to be a definitive text.

The book proceeds on the basis that the laparoscopic approach is correct and there is very little discussion on non-laparoscopic and open surgery. This may well be appropriate in the form of laparoscopic antireflux surgery and cardiomyotomy but is certainly not in the form of antiobesity surgery or surgery for cancer. The impression that the laparoscopic approach is well established is inaccurate for these latter conditions and malignancy, where open surgery holds sway. The discussion on laparoscopic antireflux surgery is limited to the 360° Nissen loose floppy wrap. The operation is described nicely with clear photographs which is a characteristic of the entire text. However, there is no discussion on the alternatives to a 360° wrap, namely a toupee 180° procedure or even the more modern partial anterior fundoplications. The various merits of these procedures would be an addition to the text as well as the role of the laparoscope in revisional surgery, and some comparison with open operations. Similarly, for cardiomyotomy for achalasia, a success rate related to open cardiomyotomy would be beneficial. Preceding these two operative sections however are two good chapters on the pathophysiology of reflux and achalasia. It is a pity in laparoscopic antireflux surgery that more comment is not made on the significant increase in the incidence of such surgery with the advent of the laparoscope. Is this a good thing or not? The pros and cons of treatment could be better discussed. With regard to cancer surgery, this really has to be emphasised as being experimental. Comparison with these success rates versus those of open surgery and a reflection on the reality of the situation, as seen in Western Europe where the disease presents at a more advanced stage, and the role of other modalities such as chemo/radiotherapy, would benefit the textbook and would expand it into a more comprehensive text. On the plus side however, the illustrations are superb and the intraoperative photographs explain the laparoscopic nodal dissection extremely clearly. It is not however a textbook of operative surgery. This book will appeal to the more specialist clinicians in upper gastrointestinal surgery and provides a cheaper and smaller alternative to the more weighty texts.

R C MASON

CORRECTION

An error occurred in the abstracts supplement *Gut* 2000;48(suppl I):A68. For abstract 254, PC Hayes was the senior author.

NOTES

Falk Workshop

The workshop entitled Update in Inflammatory Bowel Diseases will be held in Ljubljana, Slovenia, on 5 May 2001. Further information: Prof Dr S Markovič, University Medical Center Ljubljana, Division of Internal Medicine, Japljeva 2, 1525 Ljubljana, Slovenia. Tel: +386 (1) 231 6925; fax: +386 (1) 433 4190; email: sasa.markovic@kclj.si

11th International Workshop of Digestive Endoscopy, Ultrasonography, and Radiology

This workshop will be held on 17–18 May 2001 in Marseille, France. Further information: Nathalie Fontant, Atelier Phenix, 41 rue Docteur Morucci, 13006 Marseille, France. Tel: +33 (0)4 91 37 50 83; fax: +33 (0)4 91 57 15 28; email: nfontant@aphenix.com

EPGS Endosonography Live in Amsterdam

This European Postgraduate Gastro-Surgical School congress will take place on 31 May and 1 June 2001 in Amsterdam, The Netherlands. Further information: Mrs Helma Stockmann/Mrs Joy Goedkoop, European Postgraduate Gastro-Surgical School, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3926; fax: +31 20 566 6569; email: W.J.Stockmann@amc.uva.nl; website: www.epgs.nl.

33rd European Pancreatic Club

The meeting will take place on 13–16 June 2001 in Toulouse, France. A training course will be organised on 13 June on "Genomics and post genomics: developments in biomedical sciences". Further information: Dr Nicole Vaysse, Inserm U531, CHU Rangueil, 31403 Toulouse, France. Tel: +33 (0)5 61 32 24 02; fax: +33 (0)5 61 32 24 03; email: nicole.vaysse@rangueil.inserm.fr; website: www.e-p-c.org.

Gastroenterology and Endotherapy: XIXth European Workshop

This course, to introduce the experienced gastroenterologist to the growing field of therapeutic endoscopy, will be held on 18–20 June 2001 in Brussels, Belgium. Further information: Mrs Nancy Beauprez, Gastroenterology Department, Erasme Hospital, Route de Lennik 808, B-1070 Brussels. Tel: +32 02 555 49 00; fax: +32 02 555 49 01; email: beauprez@ulb.ac.be

Falk Symposium

The symposium Inflammatory Bowel Disease: A Clinical Case Approach to Pathophysiology, Diagnosis, and Treatment will be held in Bologna, Italy on 22–23 June 2001. Further information: Prof Dr M Campieri/ Dr P Gionchetti, Policlinico S. Orsola - Malpighi, Dipartimento di Medicina Interna e Gastroenterologia, Via Massarenti 9, I-40138 Bologna, Italy. Tel: +39 (051) 6364 116 or 6364 122; fax: +39 (051) 392538; email: campieri@med.unibo.it or paolo@med.unibo.it