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Reply

EDITOR,—We welcome Professor Jones' comments on our recent paper. It is a criticism that can be levelled at any clinic based study of IBS that these patients are highly selected, not least because of high rates of psychiatric morbidity. These patients do, however, merit study in their own right as they are the very patients with whom gastroenterologists, and by inference physicians in primary care, most need help.[1] Furthermore, there are practical and ethical issues to be considered. Clinic patients are readily available and amenable to being studied. A positive result in these highly selected patients is possibly a necessary prerequisite to provide the impetus to extend an investigation into less selected groups.

Encouraged by our findings on selective affective biasing in clinic patients with IBS, we are now carrying out similar investigations in subjects with symptoms of IBS drawn from the community, both consulters and those who do not, and also in patients with other physical symptoms for which no sufficient organic pathology can be shown.

The word recognition memory test methodology that we use provides a direct but covert assessment of schema driven cognitive processing. The influence of such schemata is pervasive and we would therefore expect that these biases would apply to the preception and evaluation of physical sensations in terms of illness. IBS non-consulters have been reported to dismiss or normalise their bowel dysfunction.[2,3] The heightened receptiveness to negative material that we found in this study might be the mechanism that prevents IBS consulters from doing just this.

What we therefore expect to find in our study of selective affective biasing in IBS sufferers drawn from the community is that those who have consulted will show abnormalities similar to those that we have reported in our clinic patients. As yet these results are not available. We have found on a preliminary analysis of our data, however, that the IBS consulters drawn from the community resemble clinic patients with respect to other indices. Using DSM-III-R criteria, 64% of our community IBS consulters qualified for a diagnosis of an affective disorder, which is a similar prevalence to that found in clinic populations.[3] Also there was no difference between these community IBS consulters and our clinic patients in terms of dysfunctional illness attitudes.[4] Our clinic patients may therefore not be quite as highly selected as they seem.

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Left sided colon cancer

EDITOR,—The neurobiology of diverticular disease leading to left sided colon cancer in 7159 patients (2478 men and 4681 women (*Gut* 1993; **34:** 499–502) is suggested by reversed cerebral asymmetry in women with left sided breast cancer.[1] This hypothesis is supported by the association of specific frontal asymmetries with certain immune functions, and by compulsive ruminations occurring before oculogyric crises linked to inefficient cortical circuits and abnormalities of dopamine subserving gastrointestinal protection, immunocytes, and mood.[2–5] It is also supported by the association of severe psychiatric disorders with severe acute colitis[6] and by the protective role of dopamine in preferentially maintaining splanchnic blood flow.[7] These findings suggest screening patients with diverticular disease for increased risk of malignancy by monitoring dopaminergic neurotransmission.[8]

A possible strategy is suggested by the fact that delay-dependent speeding of reaction time, reflecting motor readiness, is abolished by depletion of dopamine.[3] Therefore, future studies may evaluate cognitive consequences of dopamine agonism and antagonism at intermediate dopamine tone in a medial-frontal-striatal 'activation' system underlying response organisation[9] by monitoring behavioural correlates of mood – that is, speech hesitation and switching pauses analysed on a time base by a microcomputer. This method is supported by participatory matching of pauses in dialogues at intermediate arousal, a joint, mutually responsive rhythm,[10] and by the concept of cellular tone.[11] Remote data acquisition[10] is an efficient, unambiguous strategy to evaluate the conveyance of ideas, a task that is possibly of sufficient complexity[12,13] to assess the role of dopaminergic neurotransmission in the development and progression of diverticular disease leading to left sided colon cancer.

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Alcohol *v* epinephrine and polidocanol

EDITOR,—We have read with great interest the report by Rutgeerts *et al* (*Gut* 1993; **34:** 348–50). The authors state that 'absolute ethanol was superior to epinephrine-polidocanol, which was not significantly better than sham therapy'. As these results differ from other previous controlled studies even from the same group,[1] we would like to comment on some clinical, endoscopical, and methodological aspects that we consider of relevance.

It is worth noting that a high rebleeding rate (40%) and low haemostatic efficacy (68%) in the epinephrine-polidocanol injection group compared with the ethanol group (20% and 88% respectively) was seen, but these differences were not significant.

As noted by the authors, shock was more frequently seen in the epinephrine-polidocanol group (10 patients) than in the sham (five patients) and alcohol groups (seven patients). It is known that shock carries an increased risk of rebleeding,[2] and this could explain, at least partially, the high failure rate in the epinephrine-polidocanol group.

Apart from the type of injected substance, there are probably other factors influencing the efficacy of endoscopic injection, such as the site and size of the bleeding ulcer.[3,4] In the study by Rutgeerts *et al*, the authors consider the proportion of gastric and duodenal ulcers between groups but not their anatomical situation. Ulcers located high on the lesser gastric curvature or posterior in the duodenal wall are more difficult to reach and have a higher tendency to rebleed.[4–7] Furthermore, the size of the ulcer, probably one of the most important factors,[8] is not mentioned in the study. In this sense, it has been shown that endoscopic injection is significantly less effective in ulcers larger than 2 cm.[5]

Another remarkable aspect is that the study was designed specifically to compare both treatment groups (ethanol and epinephrine-polidocanol) with sham therapy (assuming a change in response of 75%). A much higher sample size would be necessary, however, to confirm differences between both treatment groups.

Thus, we believe that there is insufficient evidence in the study to conclude that absolute alcohol is superior to epinephrine-polidocanol. The efficacy of injection therapy is probably related less to the type or combination of substances used than to other factors, such as the size and site of bleeding ulcer. These variables should be considered in studies assessing the efficacy of endoscopic injection techniques.

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Tumour necrosis factor and platelet activating factor in stool during salmonellosis

EDITOR,—We read with interest the work of Harendra de Silva *et al* (*Gut* 1993; **34**: 194–8) reporting interleukin 6 and tumour necrosis factor (TNF) in the stool of children with *Shigella dysenteriae* infection. We are particularly interested by data reporting the absence of TNF in the stool of patients with Salmonella infection.

Platelet activating factor (PAF) is a phospholipid mediator implicated in gastric ulceration and ischaemic bowel necrosis.[1] Tumour necrosis factor generates PAF production in human monocytes.[2] A close relation has been reported between PAF and TNF in the gastrointestinal tract where PAF mediates TNF induced damage.[3,4] Platelet activating factor and TNF have been reported in the stool of patients with inflammatory bowel disease.[5,6] Furthermore PAF is released in the stool of patients with bacterial (*Salmonella*, *Clostridium difficile*) but not with viral (rotavirus, adenovirus) or parasitic (*Cryptosporidium*) diarrhoea.[7] The lack of TNF in the stool of patients with *Cryptosporidium* or rotavirus may be related to the absence of a faecal PAF. The lack of TNF in the stool of patients with salmonellosis is, however, surprising and suggests, for the first time, that in some gut inflammatory states TNF is not essential for the amplification or initiation, or both of PAF release. To confirm this hypothesis it could be of interest to assess faecal TNF concentrations, for example during *Clostridium difficile* colitis. The lack of TNF and interleukin 6 in the stool of patients with salmonellosis strengthens the putative role of PAF in the ulceration and inflammation seen in the gastrointestinal tract of these patients.

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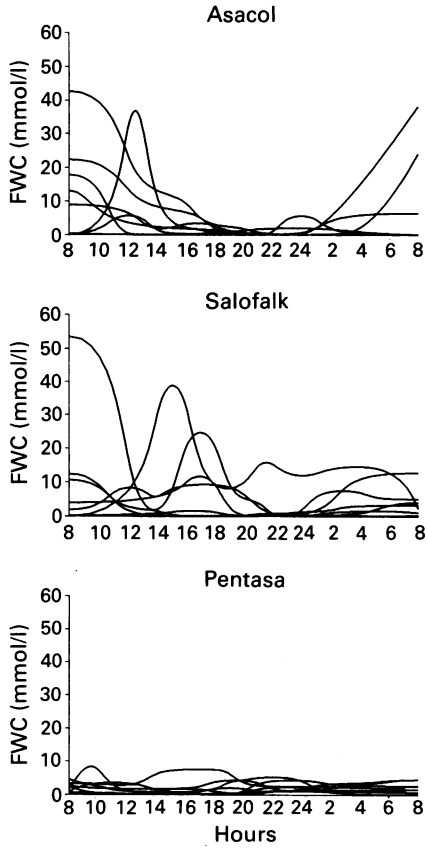
Oroileal transit of 5-aminosalicylic acid

EDITOR,—We read with much interest the elegantly performed study by Goebell *et al* (*Gut* 1993; **34**: 669–75) concerning the fate of 5-aminosalicylic acid (5-ASA) from Salofalk in the small intestine. The study elucidates some important aspects on the bioavailability of 5-ASA (pH of the gut lumen, the intestinal transit time).

We would like to comment, however, on the interpretation of the results. The authors conclude, that 30% of the ingested dose passed the ileum in solution, which is similar to the results from ileostomates on Salofalk.[1] Another 10% was found in the urine, and it is therefore concluded that 60% reach the colon in unreleased form. The design of the study does not permit this conclusion because the localisation of undissolved tablets was not assessed. In fact, some tablets could still be retained in the stomach. As the authors point out, the gastric retention time is highly variable.

Moreover, when the Salofalk tablet dissolves, its content of 5-ASA is released within 30 minutes,[2] so mean values showing that 1·5% of the content is released in the duodenum, 5·7% in the jejunum, and 12·7% in the ileum are misleading. Individual data for the six subjects would yield more accurate information.



Concentration of 5-aminosalicylic acid in ileostomy fluid. FWC=faecal water concentration.

We have studied ileostomy patients during steady state treatment with different 5-ASA preparations.[1] The subjects were given 2 g 5-ASA daily (two tablets of Salofalk (250 mg) four times daily, 400 mg Asacol five times daily, and Pentasa 500 mg four times daily) half an hour before the meals, as suggested by Goebell *et al*, and the concentration of 5-ASA was measured in the ileostomy output for 24 hours. Despite the dose being given four–five times daily, only one–two peak concentrations were seen for Asacol and Salofalk, and a lower but steady concentration during Pentasa (Figure), emphasising the importance of the size of the drug formulation for gastric retention time.

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Comparison of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma

EDITOR,—We read the report by Ziegler *et al* (*Gut* 1993; **34**: 604–10) and were impressed by the quality of the computed tomography and endogastric ultrasonograms, and by the accuracy of their endosonographic assessment of gastric tumours and node state compared with subsequent histological examination. The argument, however, which the authors use to justify their conclusion that 'endogastric ultrasonography should be introduced into the preoperative assessment of patients with gastric carcinoma' is flawed.

The authors have presented no data that support the claim of the final paragraph of their paper that 'as endogastric ultrasonography has by far the highest sensitivity and specificity for correct TN classification, the introduction of this technique in the preoperative diagnostic programme allows much better selection of inoperable patients'. They describe a comparison between computed tomography, endogastric ultrasonography, and intraoperative clinical assessment in a series of 108 patients, all of whom had total gastrectomy for their gastric tumours. They do not describe the computed tomographic findings, endogastric ultrasonographic findings or clinical assessment in any patient with inoperable tumours, and the data they present, while interesting, cannot therefore be used to support their claim relating to the selection of inoperable patients.

As clinicians, most of us would be very interested in any technique that would permit the reliable preoperative prediction of inoperability, and in some ways the paper has missed an opportunity to make an assessment of the potential clinical usefulness of endosonography. The authors must have imaging data that relate to patients who were subsequently found to be inoperable at laparotomy, and we would be very interested to see these results,