meticulous detail, and the superiority of a potent antacid, or cimetidine, over placebo is not in question. There is, however, the problem of translating the absolutes of controlled trials into the therapeutics of peptic ulcer.[7] The design of both studies favoured exaggerated remission rates for active and placebo therapy, and it is unlikely that similar rates would have been achieved had patients been enrolled on ulcer healing.

Double blind randomised, placebo controlled maintenance studies, embellished by a plethora of data on frequency of routine endoscopy, definition of ulcer recurrence, asymptomatic recurrence, smoking, duration of disease, previous active therapy etc. have, over the years, assumed an almost unchallengeable mystique. The list of variables, however, is an evolving one. *Campylobacter pylori*, parietal cell sensitivity on ulcer healing[8,9] and urinary bismuth levels[10] have recently been suggested, and to these must now be added the time interval between recent ulcer healing and entry into study. As the majority of recurrences occur within the first few months after ulcer healing, we would suggest that the time interval between healing and entry be considered before trying to compare apples with pears. Ideally, maintenance studies should only include patients enrolled immediately after endoscopic healing and withdrawal of the healing agent.

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Disturbed fibrinolysis in patients with inflammatory bowel disease

SIR,—The potentially important findings reported by Dr de Jong and colleagues (*Gut* 1989; **30:** 188–94) on fibrinolytic abnormalities in inflammatory bowel disease patients are diminished in value by misuse of statistical methods. It is claimed that the finding of a median prothrombin time of 18 s (normal range 15–19 s) in patients is so different from the median prothrombin time of 17 s in controls that such a difference would not be expected by chance if the experiment were repeated 1000 times. In a study of 28 patients with great overlap between the two groups this is clearly nonsensical.

In Fig. 2 where the actual data for plasminogen activator inhibition are shown the groups appear to be virtually identical: indeed if one performs a Wilcoxon's rank-sum test on the points there is no difference between the two groups (T1=724, T2=872), though a level of significance $p<0{\cdot}01$ is claimed.

The same considerations apply to other aspects of the data as presented and this renders the conclusions of the study invalid.

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Rebound nocturnal hypersecretion after H_2-receptor antagonist

SIR,—The recent paper by Fullarton *et al*[1] gives rise to some important criticism. There are three major points to emphasise: (1) The small number of patients (eight) enrolled and the marked individual variation of their secretory patterns (see the non-homogeneous nocturnal acid output values in the pretreatment phase) reduce the reliability of the study. This is particularly so when considering that, by simply adding two cases to the six patients of the authors' interim report,[2] median pH values of the three daytime profiles changed dramatically – for example, from pH 0·7 to pH 1·3 on treatment, and

the difference between pre and post therapy nocturnal acid outputs reached statistical significance.

(2) The pretreatment daytime median acidity profile presents pH values which are surprisingly higher than those previously published in identical profiles pertaining to duodenal ulcer patients in clinical remission.[3,4] Perhaps shortcomings in the calibration procedure or relevant drift of the glass electrodes may have been responsible for this. More coincident daytime pH profiles between the pre and during treatment groups would have also been expected in relation to the authors' statement that single evening doses of nizatidine 300 mg *nocte* only inhibit nocturnal acidity '. . . without causing any suppression of daytime intragastric pH'. On the contrary, the profile of the final day of treatment runs almost constantly below the basal one throughout the whole day and, as this happens at median pH values which are mainly between 1 and 2 pH units, the difference is very high in terms of hydrogen ion activity.

(3) When performing multiple non-parametric testing, such as the one that the authors applied on daytime pH recordings of 30 min intervals over 12 hours, the correction of the significance level of the α probability is mandatory. This omission can provide differences which are not actual or are too optimistic, especially when the number of patients is too low as in this study. As no mention of its application was made by the authors, there is some doubt as to the reliability of the significant p value ($<0{\cdot}05$) related to the mid morning and mid afternoon differences they observed by comparing the multiple 30 min periods of the three daytime pH profiles. If so, these partial differences cannot be considered as '. . . some evidence for daytime rebound hyperacidity'. Therefore, it is difficult to accept that increased acid secretion presumably caused by up regulation of H_2-receptors occurs only during the night. The fact that measurement of pH instead of acid output might have overlooked this effect during the daytime is a speculation which is a result of the adoption of two different techniques for studying the same biological phenomenon.

Although it is of great interest to establish whether rebound hyperacidity does or does not occur after stopping H_2 antagonist treatment, larger sample sizes and more rigorous methodology are required to provide a satisfactory answer to this question.

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Reply

SIR,—Dr Savarino is correct to stress the importance of confirming rebound hypersecretion after H_2-receptor antagonist therapy in larger numbers of patients. We have, in fact, recently completed a much larger study where this was confirmed at highly significant levels.[1] In addition, there has been a further study from Dr Pounder's group also confirming rebound hypersecretion after H_2-receptor antagonist therapy.[2]

There are clearly variations in intragastric acidity as measured by *in situ* pH electrodes particularly when equipment varies between centres. Our pretreatment intragastric pH profiles, in duodenal ulcer patients are certainly lower than our comparable profiles using identical equipment in healthy volunteers.[3] We would not therefore accept that we have problems with our combined glass electrodes in terms of calibration or drift as we have recently shown that the combined glass electrode (Radiometer GK 2802C) has a shorter response time, better sensitivity and significantly less drift than other electrodes.[4]

Finally, we cannot accept that more 'rigorous' methodology would provide a more satisfactory answer to the question of rebound hypersecretion. The technique used in this study allows a 24h assessment of related aspects of gastric secretory function (acidity *and* ouput) which are complimentary.

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