mucosa were not able to undergo respiratory burst. We suggest therefore that these cells which are unresponsive to interferon-gamma are 'desensitised' or downregulated. It is possible that the small proportion of macrophages from normal mucosa that are able to release oxygen radicals may enhance their production of these enzymes and metabolic events by stimulation with interferon-gamma. However, this still leaves a large proportion that did not show evidence of being able to undergo respiratory burst after stimulation.

Other studies have also shown that the macrophages from normal colonic mucosa are not able to express interleukin-2 receptors despite stimulation by interferon-gamma. In contrast, significant proportions of macrophages from mucosa with active inflammatory bowel disease expressed these receptors. That these latter cells are activated was shown by their capacity to release oxygen radicals. Macrophages isolated from mucosa with active inflammatory bowel disease also produce more interleukin-18 (IL-18) than cells from normal mucosa. Lipopolysaccharide enhanced IL-18 production by cells from inflamed mucosa but not from normal.

We suggest, therefore, that a large proportion of both normal ileal and colonic mucosa are downregulated in their capacity to perform a number of functions. This downregulation may be required under normal physiological conditions to protect against injury. As we have reported, we suggest that the enhanced functions by macrophages from mucosa with active inflammatory bowel disease -- for example, respiratory burst capacity and IL-18 production -- are due in large part to the enhanced population of cells (most likely monocytes migrating into the mucosa) which are primed or in an enhanced state of activation. In the mucosa these cells may be phenotypically different.

We do not think that prostaglandin E2 is likely to be important in priming macrophages, as studies have shown that at very low concentrations it can inhibit class II expression. Enhanced class II expression is a feature of activated macrophages.

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Intragastric acidity and serum gastrin after sufotidine

Sir,—The recent paper by Smith and Pounder (Gut 1990; 31: 291–3) shows that the new competitive H+ receptor antagonist sufotidine, taken in doses of 600 mg 3 times per day, virtually eliminated 24-hour gastric acidity. Thus its antisecretory effect closely resembles that of the proton pump inhibitor omeprazole.1 The study, however, is not without relevant methodological problems.

(1) The gastric circadian acidity pattern is characterised by high frequency regular pH fluctuations both in basal conditions and during drug induced events. These changes can be properly described with a scanning rate equal to or lower than one point per minute.

The hourly sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent manner2 and the usual acidity indexes calculated from these low frequency acquired pH profiles are almost invariably unreliable.

(2) The trapezoidal rule is a fairly robust way of calculating integrals of functions that are not very smooth, provided that the increment is several times shorter than the duration of the shortest fluctuation of the function to be integrated.3 Since the circadian pH profile shows many sharp real pH fluctuations the one hour step does not allow the use of this numerical integration method.

(3) The experimental data not included in their paper for 1000 and 2000 hours in duodenal ulcer patients, albeit clinical remission, cannot be replaced with datapoints obtained in normal subjects. More important, acidity measurements pertaining to healthy subjects are unlikely to correspond to those achieved with a very powerful H+ receptor antagonist, such as sufotidine. Moreover, since the integral of equally spaced series of data reflects the arithmetic mean, this replacement is simply useless.

(4) The authors state that the significance of the difference between the integrated 24 hour values were assessed using Wilcoxon's matched pairs signed rank test. Even in an ideal case in which all the after treatment values are lower or higher than the before treatment values, by definition a test of this type cannot provide a probability level lower than 2, k being the number of couples.

With a sample size of k = 7, as that studied by Smith and Pounder, the minimum p value one can obtain is 2 × 1/128 = 0.008. Therefore, the authors could not have found a probability level lower than 0.001. Moreover, since in one of the seven cases the median integral did not increase, it is incorrect to report a p value of less than 0.001.

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Reply

Sir,—We reject three out of four of Mela et al's criticisms.

(1) Twenty four hour intragastric acidity can be measured by either aspiration or the use of an intragastric probe. We have used the former method for the last 16 years,1 and it has been extensively described.2 It is extremely reproducible, and has provided reliable estimates of the effect of a range of antisecretory drug regimens.3 The use of a pH probe results in such an avalanche of data that Savarino and Mela could not cope with the hours of continuous intraluminal monitoring and those of simultaneous gastric aspiration appeared to be better correlated if the elimination of noise disturbing the in vivo pH-meetry curves is obviously desirable.

(2) The use of the trapezoidal rule is another type of ‘smoothing’ -- certainly the integration of observed values of either acidity or gastrin provides an easily understood measure of individual 24 hour responses.

(3) The samples for 1000 and 2000 hours were not aspirated, because they occurred immediately after a main meal and oral dosing with either sufotidine or placebo. We did not want to remove any active drug from the stomach. We know thatintragastric acidity in either patients or healthy subjects is overwhelmed at these times by food buffer (see the similar value for 1400 hours in the same experiments). The substituted values tend to underestimate the antisecretory effect of sufotidine.

(4) The results of dosing with sufotidine 600 mg 3 times per day to show that statistical analysis is almost superfluous, although we agree that the p values in Figures 2 and 4 are incorrect, and should be <0·01 and <0·05, respectively.

A wide range of techniques can be used for the mathematical and statistical analysis of 24 hour data. We believe that the advantages of our technique are that it is simple to perform and the mathematical presentation produces a clear result -- some statisticians tend to overinterpret 24 hour data. We believe that the advantages of our technique are that it is simple to perform and the mathematical presentation produces a clear result -- some statisticians tend to overinterpret 24 hour data.
Inhibition of nocturnal acidity

Sir,—We read with interest the paper by Professor Gianchi Porro and his coworkers (Gut 1990; 31: 397–400) indicating that inhibition of nocturnal acidity is important, but not essential, for duodenal ulcer healing. We also have expressed the view that inhibition of nocturnal acidity is by no means paramount in the healing of duodenal ulcers. This was, however, based on a medical treatment of duodenal ulceration and some of our data on H₂ receptor antagonists and inhibition of acidity are at variance with that of the authors.

In a study published in the British Journal of Surgery① we compared the effects of ranitidine 300 mg nocte with highly selective vagotomy in subjects with duodenal ulceration. We were able to show that, as expected, ranitidine given at night had a profound effect on nocturnal acidity but that highly selective vagotomy was a much more potent inhibitor of daytime than night time acidity. From these data we suggested that inhibition of 24 hour acidity was important in the healing of duodenal ulcers and marked pyloroplasty in individual patients as first suggested by Dragsstedt. Ranitidine is particularly effective in inhibiting 24 hour acidity when given at night and, similarly, highly selective vagotomy is effective in reducing 24 hour acidity but may not be as effective during the day. Because of these findings we were particularly interested to know whether ranitidine given in the morning would be as effective in the inhibition of 24 hour acidity as when given at night. In a study of 16 normal subjects,② we compared the effect of ranitidine 300 mg at night with 300 mg in the morning in normal subjects. This showed that although the median 24 hour pH was not marked different between the two treatment groups, the reduction in acidity afforded by night time ranitidine was significantly better than that afforded by the morning dose. This is in contrast to the conclusions of Professor Gianchi Porro et al, who were unable to show such a difference.

One reason for the difference between our findings and those of the authors may relate to the totally inappropriate method used by the authors to assess acid inhibition. The authors have calculated the area under the curve of pH v time. Since pH units are on a logarithmic scale an analysis of this type has little meaning, as Walt③ has indicated. The appropriate method of analysis is to measure the area under the curve of the hydrogen ion activity v time. The area under this curve is a measure of the 24 hour acidity and, when active medication is compared against placebo, the percentage reduction in acidity can be calculated. This is not possible using any method which involves the pH. In addition, the authors have derived means and standard deviations from the areas under the patients' individual curves in spite of this being inappropriate for any value derived from pH units. An additional criticism is that these individual values are expressed to three decimal places despite being derived from a pH electrode calibrated at room temperature. The use of parametric statistical methods for analysis, such as the Student's t test is also inapplicable as Walt③ has indicated. Indeed, it seems likely that if the authors’ data were analysed correctly as described by Walt and appropriate statistical methods applied, the conclusions would be in agreement with our own.

It is our hypothesis that although the suppression of nocturnal acidity is not the sine qua non in the healing of duodenal ulcers, ranitidine given at night is more potent than ranitidine given in the morning because it has a superior effect on suppression of 24 hour acidity. The authors' clinical results also tend to support this view, since the nocturnal treatment was superior in respect of the healing rates at two weeks. This difference did not achieve statistical significance, but as the authors indicate, this is not unexpected with such small numbers in the study. To settle this matter would require a clinical study with large numbers of patients since meta-analysis④ would predict that the difference in healing rates between the two regimes would be quite small.

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2 Patel N, Rogers MR, Primrose JN. Why do duodenal ulcer patients heal faster when H₂ receptor antagonists are given at night? Gastroenterology 1990; 98: A104.

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Annual Postgraduate Course, Common Liver Problems: An Update on Practice and Science, at the Marriott Hotel in Chicago, Illinois, 3–4 November 1990. The postgraduate course will be followed by the 41st Annual Meeting of the American Association for the Study of Liver Disease on 5–6 November 1990. For further information contact: Registration Manager, Slack Inc, 6900 Grove Road, Thorofare, NJ 08086–9447 USA. Tel: (609) 848–1000.

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