

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 reactive metabolites after 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.

Our other studies have also shown that the macrophages from normal colonic mucosa are also 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.² 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-1 β (IL-1 β) than cells from normal mucosa. Lipopolysaccharide enhanced IL-1 β production by cells from inflamed mucosa but not from normal mucosa.³ Our studies also suggest enhanced antigen presenting capacity by macrophages from mucosa with active inflammatory bowel disease.⁴

We suggest, therefore, that a large proportion of macrophages in 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-1 β production – are due in large part to the elicited population of cells (most likely circulating monocytes migrating into the mucosa) which are primed or in an enhanced state of activation. In the mucosa these cells may be phenotypically different.⁵

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.^{6,7} Enhanced class II expression is a feature of activated macrophages.⁸

Y R MAHIDA
Department of Therapeutics,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH

D P JEWELL
Gastroenterology Unit,
Radcliffe Infirmary,
Oxford

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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 H₂ receptor antagonist sufotidine, taken in doses of 600 mg bd, induces virtually 24 hour gastric anacidity. 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 real pH fluctuations both in basal conditions and during drug induced events. These changes can be properly described using a scanning rate equal to or lower than one point per minute.²

The hourly sampling rate is inappropriate to represent what is happening to gastric acidity in time-dependent measurements^{3,4} and the usual acidity indexes calculated from these low frequency acquired pH profiles are almost invariably unreliable.⁴

(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 lower than the duration of the shortest fluctuation of the function to be integrated.⁵ Since the circadian pH profile shows many rapid real pH fluctuations² 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 in 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 H₂ 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 pair 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}, k being the number of couples.⁶

With a sample size of k=7, as that studied by Smith and Pounder, the minimum p value one can obtain is 2⁻⁷=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 gastrin integral did not increase, it is incorrect to report a p value of less than 0.001.⁷

G S MELA
E CAPUTO
G VILLA
Istituto Scientifico di Medicina
Interna, Cattedra di Clinica Medica R

V SAVARINO
P ZENTILIN
Cattedra di Gastroenterologia,
Genova, Italy

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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 certain advantages. It is extremely reproducible,² and has produced 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 have concluded that 'hourly pH values 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-metry curves is obtained.'⁴

(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 that intragastric acidity in either patients or healthy subjects is overwhelmed at these times by food buffer (see the similar value for 14 00 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 bd are so clear 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 result⁵ – some statisticians tend to overinterpret 24 hour data.

J T L SMITH
R E POUNDER
Academic Department of Medicine,
Royal Free Hospital School of Medicine,
London NW3 2PF

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Inhibition of nocturnal acidity

SIR.—We read with interest the paper by Professor Bianchi 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, related to the surgical 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 Surgery*¹ 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 not particularly inhibition of nocturnal acidity, as first suggested by Dragstedt. 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 most of the effects seem to be 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 markedly 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 Bianchi 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 regimens would be quite small.

J N PRIMROSE

N PATEL

M R ROGERS

University Department of Surgery,
St James's University Hospital,
Leeds LS9 7TF

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- 2 Patel N, Rogers MR, Primrose JN. Why do duodenal ulcers heal faster when H₂ receptor antagonists are given at night? *Gastroenterology* 1990; 98: A104.
- 3 Walt R. Twenty four hour intragastric acidity analysis for the future. *Gut* 1986; 27: 1–9.
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NOTES

Register of Primary Immune Deficiencies

In line with other European countries, a register of all patients in the United Kingdom with primary immune deficiencies is being compiled. This is organised by Dr J Gooi, Immunology Department, Blood Transfusion Service, Bridle Path, Leeds LS15 7TW. In order to gain complete coverage we should be grateful if any physicians or general practitioners, who have not already been contacted and who are currently managing such patients, could send details of their patients to Dr Gooi. Registration forms are available on request from Dr J Gooi (tel: 0532 645091) or Dr H Chapel (tel: 0865 817305), Immunology Department, John Radcliffe Hospital, Oxford OX3 9DU.

Hopkins' Endoscopy Prize

The Hopkins' Prize is offered annually for a paper on any topic relating to endoscopy. Applicants are invited to submit a three page summary of the proposed paper to the Endoscopy Committee of the BSG who will recommend to Council the recipient of the 1991 award. The closing date for entries is Friday, 14 December, 1990.

Further information from: Dr N Krasner, Department of Medicine, Walton Hospital, Rice Lane, Liverpool L9 1AE.

Pancreatic Society of Great Britain and Ireland

Symposium on 'Pathogenesis of Pancreatitis' to be held 15 November 1990. Details from Joan M Braganza, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

Course in gastroenterology

A course designed for consultants and registrars, including those who do not specialise in gastroenterology, will be given on 6–9 January, 1991 in Oxford, and cover topics of current interest in relation to the normal functioning of the digestive system and its diseases. Course fee £100. Closing date for applications 1 December, 1990.

Details from Dr D P Jewell, Radcliffe Infirmary, Oxford OX2 6HE. Tel: 0865–816829.

American Association for the Study of Liver Diseases Postgraduate Course

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.

North American Society for Pediatric Gastroenterology and Nutrition

2–3 November, 1990, The Palmer House Hotel, Chicago, Illinois. For further information, registration, and housing forms, please contact: NASPGN Registration Manager, c/o Slack, Inc, 6900 Grove Road, Thorofare, NJ 08086–9447 USA. Tel: (609) 848–1000.

Sir Francis Avery Jones BSG Research Award 1991

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1991 Award. Applications (15 copies) should include:

- (1) a manuscript (2 A4 pages *only*) describing the work conducted;
- (2) a bibliography of relevant personal publications;
- (3) an outline of the proposed content of the lecture, including title;
- (4) a written statement confirming that all or a substantial part of the work has been personally conducted in the United Kingdom or Eire.

The Award consists of a medal and a £100 prize. Entrants must be 40 years or less on 31 December 1991 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Spring Meeting of the Society in Manchester in 1991.

Applications (15 copies) should be made to: The Honorary Secretary, BSG, 3 St Andrew's Place, Regent's Park, London NW1 4LB by 1 December 1990.