LETTERS TO THE EDITOR

Acute diarrhoea in expatriates in Bangladesh

SIR,—The study by Van Loon *et al* (*Gut* 1989; 30: 492–5) illustrates an important aspect of management of adult acute diarrhoea in expatriates in Bangladesh. We have completed a larger study of loperamide and dioralyte in the treatment of acute adult diarrhoea in servicemen in shore bases and ships visiting foreign ports.

Criteria for diarrhoea were two or more loose stools in the previous 12 hours. Any underlying chronic bowel disease was an exclusion to entering the study. Subjects were randomised to four treatment groups: placebo, placebo+dioralyte, loperamide, loperamide+dioralyte. The study was double blind with respect to loperamide and open with respect to dioralyte. Subjects were instructed to take two capsules (loperamide or placebo) immediately and one capsule after each further loose stool; those in the dioralyte groups took one sachet in water after each loose stool. The occurrence of vomiting, abdominal pain and loose stools were recorded on diary cards, as was their assessment of general well being.

Of 397 subjects randomised in the study only 290 had fully complete diary cards but numbers of uncompleted cards were the same in each treatment group. The 290 cards were analysed for duration of the diarrhoea, severity of the diarrhoea, time of return to normal activity and general assessment of well being. Results were analysed by non-parametric methods using a Kruskal-Wallis test for multiple groups and Wilcoxon's rank-sum test for individual treatment differences.

Duration of diarrhoea was shortest in those taking loperamide and dioralyte (mean 1.5 days) and this was significantly less than those on placebo alone (1.9) or placebo and dioralyte (1.9) (both $p < 0.01$). The loperamide alone group (1.7) was not significantly different from the other groups.

Overall the mean numbers of loose stools showed the same trend; loperamide and dioralyte was the best group (mean 4.9) and next was loperamide alone (mean 5.0). These were significantly less than the placebo and dioralyte group (7.4) although not different from placebo (6.5).

Results of time of return to normal activity and general symptomatic well-being showed a trend towards a benefit from loperamide but these data failed to reach statistical significance.

It is worth noting that Van Loon was studying the effect of loperamide on numbers of stools of patients who were all instructed to take dioralyte in addition. These findings are consistent with ours; the loperamide+dioralyte group was significantly better than the placebo+dioralyte group in terms of duration of diarrhoea and number of loose stools.

There is a continuing tendency to withhold loperamide in the treatment of acute adult diarrhoea on the basis that enteric pathogens may not be excreted. There is no good evidence for this view and it is now clear from our studies and those of Van Loon that the best treatment regime for these patients is loperamide and dioralyte. The patients we were treating had less severe diarrhoea than those treated in

Bangladesh. Van Loon points out that this is the reason the Swedish study¹ failed to show a difference between loperamide and placebo and it is clear that large numbers are needed if less severe symptoms are to be studied.

In summary the results of the study by Van Loon in severe infectious diarrhoea are corroborated by our study in patients with less severe symptoms. The type of infectious diarrhoea we studied is very common in Britain and these data should encourage prescription of loperamide and oral rehydration solutions as an effective treatment combination. Indeed, education of patients may ensure speedier and cheaper treatment for them in view of the findings that both preparations may be obtained at less than the prescription cost as over the counter medicines.²

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1 Bergstrom T, Alestig K, Thoren K, Trollfors B. Symptomatic treatment of acute infectious diarrhoea: loperamide versus placebo in a double blind trial. *J Infect* 1986; 12: 35–38.

2 Medicines that cost less over the counter. *Drug Ther Bull* 1989; 27: 42–3

Reply

SIR,—Thank you for giving me the opportunity to reply to the letter by Drs JK Ramage, ARO Miller, and PD Clarke.

I am pleased that the study by Ramage, Miller and Clarke fully supports our finding that loperamide and oral rehydration combined constitute a most effective treatment for acute watery diarrhoea in adults, thus refuting the fear of enhanced invasiveness of the pathogens involved. I should stress here again, however, that this conclusion not be extended to infants or children in the developing countries.

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Peptic ulcer in India

SIR,—We congratulate Professor M S Khuroo and his colleagues on their excellent paper concerning the prevalence of peptic ulcer in Srinagar.¹ Our earlier reviews of the distribution of peptic ulcer in India and Bangladesh preceded the advent of fiberoptic endoscopy.^{2,3} Our conclusions depended on the correlation of hospital admission rates, surgical and barium meal reports, and the experience of medical workers in a given area. It is particularly valuable now to have a prospective population survey based on endoscopic findings. It is interesting that their figures confirm that there is a high duodenal: gastric ulcer rates and a marked predominance in men.

Our findings showed a marked difference in the incidence of duodenal ulceration in rural areas between rice and unrefined wheat eating populations. The reports that we received from Kashmir also indicated that the incidence of duodenal ulcer was higher in the rice eating areas around Srinagar than in the unrefined wheat eating areas of Jammu. It would be interesting if this could be confirmed now that endoscopic facilities are available.

In our survey, we were impressed by the high incidence of early pyloric stenosis in

relation to haemorrhage and perforation in rural areas with a high incidence and which were well served by local hospitals. Over the course of time, we noticed a changing pattern in urban areas with an increasing incidence of haemorrhage and perforation, which we attributed to the greater pace and stress of city life. This pattern seems to be present now in Srinagar, although the incidence of stenosis (6.1%) is still a high figure.

We also noted that the incidence of duodenal ulcer tended to be high in the large cities in the unrefined wheat eating regions where the incidence in the surrounding rural areas was low, and again we attributed this to the added stresses of urban life. This may account for the different conclusions reached in other reports about the distribution of peptic ulcer in India because they were largely based on information obtained from urban areas.

Our particular interest was in the relationship between staple diets and the distribution of duodenal ulcer in rural areas. There is increasing evidence of a high incidence of duodenal ulcer in populations of the world where highly milled or polished rice is the staple food and of a low incidence where unrefined wheat is used.

Malhotra, as quoted, attributed this to the greater mastication required in eating unrefined foods such as chappatis as compared with a sloppy rice diet. He attached importance to the buffering effect of saliva and more recently, to its epidermal growth factor content.

Our investigations have shown that unrefined wheat⁴ and certain other foods contain a protective factor against ulceration, and that on the other hand, the oil in refined rice on storage gives rise to ketoaldehydes that can be ulcerogenic.⁵ We feel that the incidence of duodenal ulcer in a population may depend partly on a balance between dietary protective and ulcerogenic factors⁶ and that the refining of rice may be contributing to the high incidence in rice eating populations.

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- 1 Khuroo MS, Mahajan R, Zargar SA *et al*. Prevalence of peptic ulcer in India: an endoscopic and epidemiological study in urban Kashmir. *Gut* 1989; 30: 930–4.
- 2 Tovey F. Peptic ulcer in India and Bangladesh. *Gut* 1979; 20: 329–47.
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- 8 Tovey FI, Jayaraj AP, Lewin MR, Clark CG. Diet: Its role in the genesis of peptic ulceration. *Dig Dis* 1989; 7: 309–23.

Reply

SIR,—We would like to thank Dr S Tovey and Jayaraj for their encouraging comments on our paper concerning the prevalence of peptic ulcer in Kashmir.¹ The epidemiology of peptic ulcer in India had been extensively studied in the past before the advent of fiberoptic endoscopy.^{2,3} The data were collected from hospital

records, railway workers from various parts of India, and practising clinicians. All these studies revealed a significant geographical difference in the prevalence of peptic ulcer disease between the north and south of India. Peptic ulcer is uncommon in the plains of Punjab, Uttar Pradesh, Rajasthan, Madhya Pradesh and Gujarat, and common in Madras, Kerala, Mysore, Andhra Pradesh and eastern parts of India – namely, Assam, West Bengal as well as Bangladesh. It is also reported to be common in the Kashmir valley in the northern most state of India while the adjacent province of Jammu has a low incidence. These geographical differences exactly matched with the differences in dietary habits. In the low prevalence area, wheat bread (chappatti) and pulses are the staple diet and in the high incidence area boiled rice, green vegetables and highly spiced food are the staple diet. Two reasons are offered to explain the role of diet in the pathogenesis of peptic ulcer namely: (1) wheat bread (chappatti) being a dry food needed a lot of chewing and excessive production of saliva, while boiled rice is sloppy and needs very little mastication and produces little saliva. These observations were confirmed and the protective role of saliva in the causation of peptic ulcer was shown,^{2,6} and,⁷ rice contained ulcerogenic fractions and the excessive prevalence of peptic ulcer in the rice eating areas was related to these ulcerogenic factors.⁷

In 1972 the Indian Council of Medical Research conducted a nation wide study on the occurrence of the peptic ulcer in India. Six centres were selected, Kashmir valley, Punjab, Delhi, Madras, Goa, and Kanpur. This was a population based study and the diagnosis of peptic ulcer was based on radiological studies of the upper gastrointestinal tract and showed that the incidence of peptic ulcer in all the six areas was less than 1% and there was no significant geographical difference in the incidence of peptic ulcer between the north and the south. This study, as already mentioned, however, has some inherent problems in its design. The present endoscopic study revealed that the prevalence of peptic ulcer in Kashmir valley was 11% and the point prevalence was around 4%. It also revealed that the complications of peptic ulcer were as common in Kashmir as in the west. Earlier there have been many reports showing either haemorrhage, duodenal stenosis or perforation to be common in peptic ulcer in India. We believe that most of these reports were drawn from highly selected groups of patients from the hospital records and do not represent a true incidence of complications of peptic ulcer in India.

With the advent of fiberoptic endoscopy, the diagnosis of peptic ulcer has become more accurate and to further study the geographical prevalence of peptic ulcer in Indian subcontinent we need to do similar studies in the plains of Punjab, and in south and eastern parts of India. Should geographical difference in peptic ulcer be confirmed by these studies, most likely explanation would be differences in the diet of these populations. The problem in doing such studies would be to select highly dedicated field staff and endoscopists and the acceptability of the population under study to undergo endoscopies. Public awareness of peptic ulcer occurrence is important and to increase the responder rate small medical centres need to be started in these areas to treat minor ailments. The press, television and the radio need to educate the public about the importance of these studies. These methods were used in our study to gain the support and confidence of the general public, and to increase the responder rate for endoscopies.

The Indian Council of Medical Research and other national research committees in India need to look into these aspects in order to start a multicentric endoscopic study on the prevalence of peptic ulcer in India. It will go a long way to finally solve the question of geographical distribution of peptic ulcer in the Indian subcontinent, and will formally establish the role of dietary factors in the cause of peptic ulcer.

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Short bowel syndrome and somatostatin 201–995

SIR,—I was interested to read the paper from S Jarnum's group (*Gut* 1989; 30: 943–9), suggesting that in patients with severe short bowel syndrome, the somatostatin analogue SMS 201–995 could increase net absorption of water sodium after reduced secretion of digestive juices rather than by increasing absorptive capacity. The authors did mention our study¹ of a patient with pancreatic cholera (vipoma) in whom the continuous intravenous infusion of 8 µg/kg/h cyclic somatostatin 14 had a dramatic effect on diarrhoea. They did not, however, quote the perfusion study of water and electrolyte movements we performed in the small bowel of this patient and of healthy control subjects. We found that in controls the decrease in intraluminal water and sodium flow rate within the distal ileum seen during somatostatin infusion was mostly accounted for by the sharply reduced entry of water and electrolytes from the duodenum into the jejunum. This finding agrees with the author's hypothesis on the mechanism of action of SMS 201–995 in the short bowel syndrome. In the patient with vipoma, however, not only the entry of water and sodium into the jejunum was reduced, but also the jejunal fluid secretion was markedly decreased, in parallel with the return to normal values of circulating vasoactive intestinal peptide. Thus, extrapolation of pharmacological findings in normal subjects to patients with various causes of diarrhoea should be cautious.

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- 1 Ruskoné A, René E, Chayvialle JA, *et al*. Effect of somatostatin on diarrhea and on small intestinal water and electrolyte transport in a patient with pancreatic cholera. *Dig Dis Sci* 1982; 27: 459–66.

Reply

SIR,—We thank Professor Rambaud for his comments on our paper.¹ Professor Rambaud's group has found, that somatostatin infusion in normal subjects decreases small intestinal flow to the distal ileum, mainly by reducing water and electrolyte entry from the duodenum to the jejunum. In contrast, a patient with vipoma showed decreased jejunal secretion as well.² They conclude, that extrapolation of pharmacological findings in normal subjects to patients with various causes of diarrhoea should be made cautiously, a conclusion to which we fully agree.

Five of the six patients we studied had inactive Crohn's disease. It has been shown, that the relative frequency of various endocrine cells and the distribution and frequency of peptide containing nerve fibres in the gut do not differ between patients with Crohn's disease and controls.³ Patients with small bowel resection have shown increased release of several gut hormones after a test meal.⁴ At present it is, however, difficult to ascertain the integrated effect of the altered hormone response on gastrointestinal secretions. We found that the reduction of stomal output during supply of SMS 201–995 in a patient with only 40 cm jejunum left was equal to the reduction in patients with longer small intestinal remnant. It is therefore possible, although not investigated in our study, that the main effect of SMS 201–995 in our patients, like in Professor Rambaud's normal subjects, was a reduction of gastroduodenal and pancreaticobiliary secretions rather than a reduction in jejunal secretions.

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NOTES

Pancreatic Inflammatory Disease Cell Biological Concepts and Therapeutic Applications

An international workshop will be held in Marburg, West Germany on 26 and 27 April, 1990. For further information please contact Prof Dr G Adler, Zentrum Für Innere Medizin, Baldinger Str, D-3550 Marburg/L, Federal Republic of Germany.