LETTERS TO THE EDITOR

Omeprazole in gastric and duodenal ulcers

SIR,—In their interesting multicentre trial (*Gut* 1990; 31: 653-6), the Cooperative Study Group concluded that omeprazole 40 mg heals gastric and duodenal ulcers more rapidly than ranitidine 150 mg twice a day, and this result may be due to the more effective control of gastric acid secretion by omeprazole. Although there is no doubt that omeprazole causes a more profound and prolonged acid inhibition than ranitidine at the above doses, part of the conclusion does not seem to be sustained by the experimental findings. In fact, while the differences in healing rates were significantly higher for omeprazole at both two and four weeks of treatment in duodenal ulcer patients, the same was not true at both four and eight weeks in gastric ulcer patients. It may be argued that the number of gastric ulcers was so small that a type II error is responsible for the lack of significant difference and, in fact, it was pointed out that the healing rates in the study are in accord with those obtained by Walan *et al.*¹ who showed in a much larger trial on gastric ulcer patients that omeprazole is significantly more effective than ranitidine.

We believe, however, that another critical point is worth emphasising. Once again we have a study which provides no information about the location of the ulcer crater in the stomach. In using a powerful antisecretory drug, such as omeprazole, it can be expected that its pharmacological effect is greater in cases associated with increased acid secretion. Unlike duodenal ulcers, gastric ulcers have normal or reduced levels of acid secretion compared to control subjects² and, although patients with gastric ulcer respond to antisecretory treatment, the relation between acid inhibition and gastric ulcer healing is not as clear cut as it is for duodenal ulcer.³ The most plausible explanation for this is that acid plays a smaller part in the pathogenesis of gastric ulcers than in duodenal ulcers. The functional heterogeneity of gastric ulcers is particularly striking in relation to the site of the niche and, using continuous pH monitoring,⁴ we recently found that the 24 hour gastric acidity of patients with ulcers located at or above the angulus is much lower than that of control subjects matched for sex and age⁵ and of patients with prepyloric ulcers.⁶ Thus the circadian acidity pattern⁷ of proximal gastric ulcers should be clearly distinguished from that of distal ones, and assessing the efficacy of potent antisecretory drugs in the whole group of gastric ulcers, independently of their location in the stomach, may be misleading. This seems to be confirmed by the results of another recent large clinical trial comparing omeprazole 30 mg and cimetidine 1 g/day in patients with only gastric body ulcers.⁸ There was no significant difference between the healing rates obtained with the two drugs, even though the dose of 30 mg omeprazole has been shown to cause a maximal decrease in 24 hour gastric acid secretion.⁹ This means that extreme acid inhibition is of no help in conditions characterised by low acid secretion, and the differences in acid secretory patterns in the populations sampled in the various clinical trials are likely to be responsible for the conflicting results of

Gastric ulcer healing

	No			Total	Healed (cum %)		Not healed Week 8
	L	M	S		Week 4	Week 8	
Omeprazole:							
Body ulcer	2	8	3	13	10 (77)	1 (85)	2
Prepyloric ulcer	1	1	1	3	3 (100)	0 (100)	0
Ranitidine:							
Body ulcer	7	4	7	18	10 (56)	5 (83)	3
Prepyloric ulcer	1	3	2	6	4 (67)	1 (83)	1

L=large >15 mm; M=medium 10-15 mm; S=small 5-9 mm.

the efficacy of omeprazole in gastric ulcers.¹⁰

Since we are still unable to give well defined guidelines for an aetiological treatment of peptic ulcer, antisecretory treatment should take into account at least the varying pathophysiological profiles of acid production in this heterogeneous disease. And there is increasing evidence that gastric ulcers can be subdivided according to their anatomic locations, which are associated with different circadian acidity patterns. Thus universal regimens with high doses of omeprazole, the most potent antisecretory drug, are unlikely to be valid for all patients with gastric and duodenal ulcers. On the other hand, individualised treatment related to the predominant pathogenetic mechanism in each patient remains at present a remote possibility. Therefore, a reasonable alternative may be to tailor the antisecretory regimen to several subsets of peptic ulcers established on the basis of their site and function.

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Reply

SIR,—Savarino and colleagues ask if healing rates in our patients with gastric ulcer could have been influenced by the ulcer site. The data on site and initial ulcer size are shown in the

Table, but the numbers are too few for valid statistical analysis.

At week 4 seven of the nine prepyloric ulcers but only 20 of the 31 body ulcers had healed. There has been speculation that gastric body ulcers heal more slowly than prepyloric ulcers because they are generally larger. No conclusion can be drawn from our data, but of the four unhealed body ulcers one omeprazole and two ranitidine treated ulcers were large. The one ranitidine treated unhealed prepyloric ulcer was large.

Separation of the data for body and prepyloric ulcers gives healing figures essentially the same as those reported in our paper for the combined gastric ulcer group.

The gradient of acid secretory levels in the healing of duodenal, prepyloric, and gastric body ulcers has been discussed for a very long time.¹ We addressed this point in our paper by speculating that, even without initial hypersecretion, effective acid suppression in gastric ulcer patients could favourably affect the balance between aggressive and defensive factors. Because the common factor for omeprazole and ranitidine is the ability to inhibit acid secretion, with omeprazole the more effective, as acknowledged by Savarino and colleagues, we adhere to our original conclusion which is still compatible with the gastric ulcer data subdivided for ulcer site. Overall these results suggest that duodenal and gastric ulcers heal more rapidly during omeprazole treatment, which may be explained by a more effective control of gastric acid secretion.

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Screening for colorectal cancer in ulcerative colitis

SIR,—We read with great interest Dr Gyde's exhaustive and critical review on how to approach the risk of colon cancer in ulcerative colitis (*Gut* 1990; 31: 1089-92). The criticism of how scarce resources are best spent seems pertinent in a disease where colon cancer, although the single most important risk factor in the longterm prognosis, accounts for only 5-14% of all deaths in ulcerative colitis.¹ The increased cancer risk is well established but probably lower than previously thought.²⁻⁴

The basic problem in evaluating screening procedures in cancer surveillance, as pointed out in the review, is the prospect that a true randomised prospective study will never be

done.' So what else is left to be done? Since surveillance experience now amounts to long periods, 15 years in our institutions, a case-control study with carefully selected control subjects from an epidemiologically defined but unscreened patient population might answer the important question: Is there a difference in deaths in colorectal cancer between 'screened' and 'unscreened' patients? Such a study is now in progress. Meanwhile, the clinicians have to deal with the potentially worrisome problem of what to do with the patients. This is probably the main reason for the widespread use of 'cancer surveillance,' although a lack of conformity in surveillance procedures may account for some of the different results. The leading article concludes, however, that we should not go on as we are, but it really offers no options.

'Routine clinical care' in patients with longstanding colitis seems a vague term with ill defined aims where patient compliance might be quite low.⁶ It also runs the risk of falsely assuring doctor and patient alike that the patient's cancer risk is being controlled when it is not.

Prophylactic colectomy in patients selected on statistical grounds (extensive disease, long duration, young age at onset), which has been advocated since the 1960s, still awaits a study proving its benefits. Even a small postoperative mortality would affect the results in a negative direction.

Although 'cancer surveillance' as reported from our group⁸ shows good compliance, that DNA aneuploidy seems a promising marker, and that a yield of incurable cancers is lacking, it seems a long way to go before a consensus can be reached in the medical community on the approach to the cancer risk in ulcerative colitis.

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Reply

SIR,—Dr Broström and colleagues are quite rightly asking 'where do we go from here' concerning the care of patients that are at high risk of developing cancer at a young age. I was not suggesting that we should withdraw the present screening procedure using 'dysplasia' as a marker. I was, however, suggesting that

clinicians still have an obligation to their patients to test the effectiveness of this screening procedure in reducing mortality, since proper randomised trials were not established before the introduction of the procedure on a wide scale.

Case-control studies can give valuable information, as Dr Broström suggests, but such studies, being non-experimental in design—that is, no randomisation with prospective follow up—are difficult to evaluate in terms of the effect of screening on mortality. They are subject to inherent biases in the groups under review which are difficult to estimate.

Case-control studies were used in some of the trials to study the effect of screening on mortality from breast cancer.¹⁻⁴ One of the case-control studies contradicted the findings of the randomised trials, which throws doubt on the findings in that particular case-control study.

One option worthy of serious consideration is to pursue the idea of a randomised trial, screening both groups but using different 'markers' for cancer in each group; for example, after randomisation, one group could be screened using 'dysplasia' as a marker and the other group screened using 'aneuploidy' as a marker. In this way no patient would go unscreened; compliance would not then be a problem and survival from cancer in the two groups could be compared.

I, however, still think a pilot study should be attempted to assess the uptake for a randomised trial into 'screened by dysplasia' and an 'unscreened' group, the unscreened group continuing to undergo routine surveillance for their disease which would include regular sigmoidoscopy, rectal biopsies, and barium enemas. ('Routine clinical care' can be carefully defined and need not be, as Dr Broström suggests, a 'vague term with ill defined aims.')

The 'screened' group would have in addition to this well defined 'routine clinical care,' regular colonoscopy, and multiple biopsies to detect 'dysplasia' in the colon.

The problem with a trial 'screening' both groups using, for example, 'dysplasia' and 'aneuploidy' as two markers tested against each other, is that unless there is an 'unscreened' control group one would not know if either marker was making a significant difference to survival compared with an 'unscreened' control group, whatever they showed as markers in comparison with one another.

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SIR,—In her leading article Dr Gyde applies the logic of a public health physician. Such an approach is welcome and she is right to say that the success of a surveillance programme can be judged only by its effect on cancer mortality. In some respects, however, her logic is neither as critical nor as rigorous as it appears.

In the opening paragraph there is reference

to cancer 'screening' among 'apparently healthy members of the population' and a quotation then draws an ethical distinction between investigation of patients who seek medical advice and of symptomless subjects on the initiative of doctors. The context suggests that patients with colitis fall into the second group of symptomless subjects. This is not so. Patients with colitis attending a clinic seek medical care for all aspects of their illness including advice about the cancer risk. It seems better to use the term 'surveillance' for clinical supervision of patients known to be at high risk of carcinoma and 'screening' for investigation of the asymptomatic general population.

Dr Gyde then draws a distinction between a group of patients, the 'non-screened group' receiving 'ordinary clinical care (which would of course include standard investigations such as sigmoidoscopy and barium enema, when deemed necessary),' and a 'screened group.' The only difference between the groups is that colonoscopy with multiple biopsies is performed in the latter. Dr Gyde advocates randomisation of patients into one of these two groups to measure the effect, if any, of colonoscopy on cancer mortality.

If such a trial were undertaken it would be necessary to obtain informed consent from each patient before randomisation. A survey among our patients has shown that few would accept random allocation when subsequent surveillance might be restricted to sigmoidoscopy. The mortality from colorectal cancer among patients with extensive colitis who are not treated by colectomy is likely to be about 8% during the period 10 to 25 years from onset of disease.¹ This figure is lower than the incidence of carcinoma because at least one third of patients who present clinically with a tumour are cured by surgery. No cancer surveillance programme will ever be completely effective due to problems outlined by Dr Gyde. To detect a reduction in mortality from, say, 8% to 3% at a significance level of 0.05 with a 75% chance of success would require two groups each of about 500 patients. The rate of acquisition of patients would be slow, many would drop out when they are treated surgically for chronic colitis or coincidental illness occurs, and follow up would have to continue for at least five years after the last diagnosis of carcinoma to avoid lead-time bias. The prospect is daunting.

A more realistic and important comparison of mortality would be between patients who regularly attend a gastroenterological clinic for supervision of their colitis and unsupervised patients who attend only when symptoms cause concern. The ethical problem would be resolved because one group wishes to attend regularly and the other does not. There are data suggesting that patients who attend for supervision have a reduced mortality from acute colitis,² the potential mortality of which must never be forgotten and is probably greater than from carcinoma. Such an analysis would test the cost effectiveness of regular supervision and would contribute knowledge about the economics of health care in this chronic disease. The relative contributions of sigmoidoscopy and colonoscopy to the detection of precancer and cancer could be analysed in the group under supervision.

In her analysis of difficulties in the definition and detection of dysplasia Dr Gyde fails to mention the fact that dysplastic lesions (and carcinomas) are often elevated from the mucosal surface. For example, among 28 operative specimens with dysplasia but no carcinoma, 20 had elevated lesions.³ Since such elevated areas may be apparent on endoscopy,