LETTERS TO THE EDITOR

Omeprazole in gastric and duodenal ulcers

Str,—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 now ubi inject 24 hour gastric acid secretion is profoundly reduced 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 significant; the assay was that the number of gastric ulcers was too small so 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 two groups were obtained by different methods. Therefore, a reasonable alternative may be to tailor the antiseptic regimen to some subsets of peptic ulcers established on the basis of their site and function.

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Reply

Str,—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 site were 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 and prepyloric 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 be achieved by 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 ulcer ulcers may be treated 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

Str,—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 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. The increased cancer risk is well established but probably lower than previously thought.1,2

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

<table>
<thead>
<tr>
<th>Gastric ulcer healing</th>
<th>No</th>
<th>Healed (cum %)</th>
<th>L</th>
<th>M</th>
<th>S</th>
<th>Total</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Not healed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body ulcer</td>
<td>8</td>
<td>3</td>
<td>13</td>
<td>10</td>
<td>77</td>
<td>1 (85)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepyloric ulcer</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>100</td>
<td>0 (100)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body ulcer</td>
<td>7</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>56</td>
<td>3 (83)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepyloric ulcer</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>67</td>
<td>1 (83)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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


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The basic problem in evaluating screening procedures in cancer surveillance, as pointed out in Dr Gyde’s 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 long-standing colitis seems a vague term with ill defined aims where patient compliance might be quite low. 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 group1 shows good compliance, that DNA aneuploidy seems a promising marker, and that a yield of incurable cancers in certain groups 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

Sr.—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 withhold 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. These 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. All 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 the 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. However, 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 an additional act 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 the 'unscreened' control group, whatever they showed as markers in comparison with one another.

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Sr.—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, the speculations in this article are 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 with colitis not undergoing 'ordinary clinical care' (which would of course include standard investigations such as sigmoidoscopy and barium enema, when deemed necessary),1 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. In this context 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%–10% around the age group 70 to 75 years of age.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 mortality trial has ever shown a benefit from any form of surveillance. 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 25 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, and the other does not.1 It is also 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 operable specimens with dysplasia but no carcinoma, 20 had elevated lesions.3 Since such elevated areas may be apparent on endoscopy,
Screening for colorectal cancer in ulcerative colitis

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