simply pass through it as suggested previously.[2 3] Concerning *M paratuberculosis*, however, the conflicting results were reported by Elsaghier *et al*.[4] They showed significantly increased antibody concentrations to *M paratuberculosis* specific protein in Crohn's disease patients. This difference might result from the antigens used for their experiments. Stainsby *et al* used antigens that were filtered sonicate preparations of the mycobacterial species, and as they discussed in their article, the study of humoral immunity to *M paratuberculosis* in Crohn's disease should be devoid of the cross reactive nature of mycobacterial antigens. Furthermore, Sanderson *et al* reported that *M paratuberculosis* DNA was identified in 26 of 40 (65%) Crohn's disease, in one of 23 (4·3%) ulcerative colitis, and in five of 40 (12·5%) control tissues by PCR.[5] We agree with Sanderson *et al* that this high frequency of identification of *M paratuberculosis* in Crohn's disease could not be explained by secondary invasion of a previously damaged mucosa. Therefore, some kinds of mycobacteria may be ubiquitously distributed in the human intestine, but *M paratuberculosis* might participate in the pathogenesis of Crohn's disease.

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Helicobacter pylori infection

EDITOR,—The EUROGAST Study[1] provided impressive confirmation of the geographical association between *Helicobacter pylori* infection and gastric carcinoma.[2]

The technique was serological, however, and necessarily considered geographically and ethnically disparate populations, so subgroup analysis for risk factors in *H pylori* infection may not be appropriate.[3]

It is known that serology does not always correlate well with active infection in apparently healthy subjects, and may merely provide a historical record.[4]

The 17 groups studied had between 132 and 229 subjects each, who presumably could have been from a variety of racial groups in the 13 different countries: these factors are well known to affect prevalence. The absence of a sex effect, and the increased frequency of infection at age 55–64 years compared with 25–34 years, harmonises well with the conclusions in other studies, and are easy to prove. But whether the technique is suitable to make statements about smoking and alcohol use is much more doubtful.

We used a reliable direct urease test (CLO test) for assessment of active *H pylori* infection in local British white patients to assess the effect of personal habits.[5] For the current cigarette smokers there was a clearly increased prevalence of *H pylori* infection (49·6% *v* 35·5% in non-smokers or those who had given up smoking at least a year before, $p<0·01$). This would be consistent with the known suppressive effects of smoking on immune defences; and also the association between peptic ulcer and smoking, as duodenal ulcer is uncontentiously very strongly associated with *H pylori*. Ours is the only study directly focused on this problem in a large homogeneous well defined population using an effective direct method for active *H pylori* infection.

I would like to persuade colleagues that this is indeed the correct answer and challenge doubters to produce a similarly coherent specific study devoted to this problem.

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Reply

EDITOR,—One aim of the EUROGAST study was to identify risk factors for *H pylori* seropositivity, using a common protocol to collect blood samples and questionnaire data from random samples of the general population in a wide range of different countries. Bateson criticises one conclusion from the study: that *H pylori* infection, as assessed by serology, is not associated with smoking.[1] He states that serology may be a poor indicator of current *H pylori* infection and that the use of different populations, with different prevalence rates, precludes general conclusions concerning risk factors for *H pylori* infection.

The lack of association between *H pylori* and smoking was seen in the whole EUROGAST population[1] and not in a subgroup analysis as indicated by Bateson. Furthermore, in none of the 17 individual centres was there a statistically significant association between smoking and *H pylori* seropositivity. The estimated odds ratio for smokers *v* non-smokers was 1·0 or higher in 10 study centres and was lower than 1·0 in seven centres (data available on request). This conclusion is consistent with the other large, population based studies that have investigated smoking in relation to *H pylori* infection, assessed by serology,[2] by serology and the urea breath test,[3] and by serology and histology.[4] The last two studies[3 4] used measures of current infection in addition to serology. Moreover, there is evidence suggesting that *H pylori* infection is most commonly acquired in early childhood[5 6] – that is, before most subjects take up smoking.

Those studies that have investigated the association between *H pylori* and smoking in patients undergoing endoscopy have variously reported a positive,[7–9] negative[10] or no[11 12] association.

The use of symptomatic patients may, however, lead to a spurious, non-causal relation between *H pylori* and smoking because both *H pylori* infection and smoking are independently related to gastric disease, especially peptic ulceration. The separate associations between *H pylori* and peptic ulceration and between smoking and peptic ulceration do not imply that there is an association between *H pylori* and smoking. Rather, it is plausible that smoking may increase the risk of disease in an *H pylori* infected subject.[13]

With regard to the use of serology to assess *H pylori* infection the evidence suggests that, in the absence of treatment, *H pylori* infections will persist for life.[14] The conclusion by Meyer *et al*, cited by Bateson, that spontaneous eradication of *H pylori* might commonly occur in healthy subjects,[15] was later retracted because of the low specificity of the serological test used in their study.[16] The only subjects likely to be seropositive in the absence of a current infection are those with severe gastric atrophy or intestinal metaplasia or both, as *H pylori* infection cannot persist in such conditions.[17] Such subjects would, however, be uncommon in the EUROGAST population where subjects were all aged under 65 years.

In conclusion, results from all of the population based studies weigh against the hypothesis that smokers are at an increased risk of *H pylori* infection. We would also suggest that patient groups may be an inappropriate population in which to study this relation.

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Aldehyde disinfectants and health in endoscopy units

EDITOR,—I read with interest this report and would accept that it considers the main issues in an effective and commonsense way. I would, however, question the statement that where an employee develops occupational asthma after exposure to glutaraldehyde and continuing exposure cannot be avoided, that the employee must be made aware of the risks of continuing exposure. The implication is that the worker is left the choice as to whether they can continue being exposed to glutaraldehyde. The employer through its occupational health department has a responsibility to advise on fitness for work. In a case where asthma has been shown to be caused by glutaraldehyde it is not reasonable to leave the decision about continuing exposure with the employee, however well informed. The employer has the responsibility for protecting an employee's health. In these circumstances redeployment and retraining may be the best outcome that an employee can expect. The report drew attention to the need for pre-employment health assessment suggesting enquiry about asthma and other conditions. The authors did not comment on whether subjects with pre-existing asthma should be employed in jobs where exposure to glutaraldehyde may occur. This is a difficult issue that seems to have been avoided.

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Reply

EDITOR,—Dr Stevens makes two main points in his letter. Firstly – what is the management of a member of the endoscopy staff who develops glutaraldehyde related asthma?; secondly – what is the recommendation of the working party regarding employment of people with pre-existing asthma who will be required to work with glutaraldehyde?

We would like to point out that it was not within the remit of the working party to produce a manual detailing how health and safety policies might be implemented. It was assumed that individual hospitals will take steps to comply with COSHH regulations.

With regard to the first point, Dr Stevens has interpreted the report as leaving it up to the subject to decide whether he or she should continue to work with glutaraldehyde. We feel this is an extreme interpretation of what has been said. The report states quite clearly that further exposure to glutaraldehyde should be avoided, but recognises that there may be circumstances when this is not possible or desirable. We have to assume that the development of occupational asthma in a member of staff working in an endoscopy unit will inevitably involve the local occupational health department, which will make an appropriate risk assessment and also inform the hospital management. This would take away the decision from the affected subject and give the responsibility to management.

It is reasonable to assume that any such decision will not be made in a vacuum. If the diagnosis of occupational asthma resulting from glutaraldehyde is definite and exposure to glutaraldehyde will probably continue, the employee should be removed from that working environment. If exposure can be reduced, however, and it is the considered opinion of the medical experts that continuing to work in the environment is not a significant risk to the employee, and there is no suitable alternative workplace such that the subject wishes to continue to work in that environment, having been made aware of the pros and cons of doing so, we believe this is a suitable plan of action. The final decision would have to rest, however, with the manager of that department.

With respect to the issue of employing people with pre-existing asthma in jobs where exposure to glutaraldehyde may occur, we believe it would have been inappropriate for the working party to be more specific than it has been, consistent with its stated intention to formulate recommendations rather than instructions. Once again a risk assessment would have to be carried out to take account of the severity of the asthma and the likelihood of exposure to glutaraldehyde. The final judgement about fitness to work is the responsibility of an occupational physician and we did not think it was the role of the working party to preempt this.

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Correlation of PCNA with bromodeoxyuridine

EDITOR,—We noted with interest the paper by Weisgerber *et al* (*Gut* 1993; **34:** 1587–92) on proliferation cell nuclear antigen (PCNA) and its correlation with bromodeoxyuridine (BrdU). We would like to express our reservations about their conclusions. The most important one is the authors' decision to only count the 'strongly stained nuclei' in the PCNA assay. This necessarily makes the assay highly subjective because of the difficulty of maintaining an identical standard for every nucleus that is assessed. The assay could only become reproducible in large numbers if either all stained nuclei were counted as positive, or if some form of extremely sophisticated image analysis system that could differentiate stained nuclei on the basis of intensity and colour of their staining was used.

While a significant correlation between the two methods assessed has been shown, the analysis has been performed on only 17 values. The correlation coefficient of 0·6 and Figure 1 shows the rather vague interrelation between PCNA and BrdU in this context. This is more important than the non-significant difference seen between the mean proliferation indices for two reasons. Firstly, there is ongoing debate about which fraction of the replicating population of cells PCNA measures – that is, the growth fraction, as in Ki67 labelling, or the S phase fraction as in tritiated thymidine or BrdU labelling. It may be dependent on the form of tissue fixation.[1–3] This study cannot identify which proliferating component has been labelled with this particular assay. Secondly, if there was a strong numerical relation between the two measured values for a given sample, then some form of paired statistical analysis would be appropriate. No evidence is given that this sort of test has been performed in this study.

We do not feel that this paper does show a close relation between the PCNA and BrdU assays. We believe it is necessary to assess a greater number of biopsy specimens taken from a much greater number of subjects; to score all PCNA stained nuclei; and place more emphasis on the correlation between the assays rather than the actual numerical values measured.

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Reply

EDITOR,—We appreciate the critical evaluation of our paper by Wilson and Schofield. We agree with most of their comments, some of which have already been considered in the discussion of our article.

In an attempt at trying to mimic an S phase marker by counting only strongly stained nuclei in the PCNA assay, the evaluation procedure certainly has to be highly standardised and the best way is by use of image analysis. If this standardisation cannot be used, it may be a better alternative to include all labelled cells in the PCNA analysis. The inclusion of all labelled cells in the PCNA assay, however, does not result in a significant correlation between the two markers in our study. We could possibly show such a correlation with a greater number of subjects, as suggested by Wilson and Schofield, and we agree that this correlation is