that potent inhibitors of gastric acid secretion should be prescribed with caution in these patients, or in conjunction with fluconazole or nystatin.

The clinical relevance of oesophageal candidal growth after gastric acid inhibition in patients with systemic sclerosis is still unclear. Zamost et al. studied two groups of such patients, one with erosive oesophagitis and impaired oesophageal peristalsis, and one without oesophagitis but with impaired peristalsis in about half the cases. The percentage of patients with positive fungal culture of oesophageal brushing was greater in the first group than in the second, although not significantly so. Moreover, positive smears with hyphae were found only in patients with erosive oesophagitis and oesophageal strictures. Thus, impaired oesophageal peristalsis, oesophagitis or oesophageal strictures may favour fungal growth in patients with systemic sclerosis. If this hypothesis is true, the increased frequency of positive cultures for Candida albicans reported by Hendel et al. in their subgroup of systemic sclerosis patients treated with acid inhibitors may result not only from the effect of treatments but also from the higher frequency of severe oesophageal involvement in this group of patients in comparison with controls. In fact, all patients receiving gastric secretion inhibitors had manometrically proven impaired oesophageal motility and abnormal gastro-oesophageal reflex whereas the control group consisted of consecutive patients with systemic sclerosis not requiring anti-reflux treatment in whom the frequency of oesophagitis and oesophageal motor dysfunction was not reported but was expected to be less than 60%.

Whatever the cause may be that favours candidal growth in the oesophageal lumen of patients with systemic sclerosis, what is the clinical relevance of this growth? Hendel et al. did not find mucosal invasive candidiasis in any of their patients. Eradication of candidal growth by nystatin or fluconazole did not influence the severity of oesophagitis, and did not further relieve reflux symptoms prevented by anti-reflux treatment. On the other hand, gastric mucosal erosions and an increase in serum alkaline phosphatase were seen after fluconazole treatment.

Patients with systemic sclerosis, impaired oesophageal peristalsis and oesophagitis may report reflux symptoms that are often severe, and oesophageal strictures and bleeding may complicate oesophagitis in some of them. Symptoms and endoscopic oesophagitis improve after gastric acid inhibition, and the risk of complications are possibly reduced by this treatment. On this basis we will continue to use potent gastric acid inhibitory drugs in patients with systemic sclerosis and oesophageal involvement.

The patient studied by Hendel et al. in oesophageal candidiasis of these patients, the best level of gastric acid inhibition that should be reached to minimise adverse events and to ameliorate the symptoms and prognosis of oesophagitis, and finally the clinical consequence of endoscopic treatments in patients with systemic sclerosis should be defined by appropriate controlled trials.


**Tumour necrosis factor α in inflammatory bowel disease**

**EDITOR—**Murch et al (Gut 1993; 34: 1705-9) show clearly that tumour necrosis factor (TNF) containing cells, probably macrophages, are clustered in the upper mucosa in ulcerative colitis and are distributed more randomly, and apparently diffusely, in Crohn's disease. Unfortunately, the legends to their colour figures do not match with the figures. Nevertheless, their assertion that there is periarthritis infiltration by TNF positive cells ('vasculopathy') may be true. In their discussion they review much evidence for why this could have been powerfully towards thrombosis in this situation.

The situation cannot, however, be simply explained in these terms. If there were such powerful promotion of thrombosis one should surely see this as a dominant feature of Crohn's disease. In practice, thrombosis of either small or large blood vessels is only rarely seen in Crohn's disease and what evidence there is for it depends on the use of special techniques.

The work of Murch et al is an important contribution to our knowledge of the pathogenesis of inflammatory bowel disease, but caution should be exercised in its interpretation.

1 C TALBOT St Mark's Hospital, London EC1V 2PS

**Reply**

**EDITOR—**We thank Dr Talbot for his generous assessment of our paper. I must apologise for the mislabelling of our figures, which occurred in press.

Dr Talbot raises what may be a central point in the understanding of the pathogenesis in Crohn's disease: what is the extent of vascular thrombosis, and how much does it contribute towards physiological disturbance and tissue changes? I fully agree that vascular thrombosis is not commonly seen in routinely stained specimens, and that special techniques are required to give a true picture of the extent of vascular involvement. When these are used, a very different picture emerges, in which multiple microvascular events are clearly occurring. The extent of vascular abnormality in Crohn's disease has been incontrovertibly shown by Wakefield's perfusion-fixation study in the very clear message from this work is that most of the vascular abnormality occurs at a level too deep to be detected in a study of endoscopic biopsy specimens. While vascular thrombosis is not recognised in Crohn's disease, it is probable that only sizeable vessels will leave detectable remnants after thrombosis. When vascular endothelial remnants are specifically hunted they are numerous, and we have additionally shown widespread attenuation of endothelial heparan sulphate in apparently healthy vessels. We would thus contend that failure to detect microvascular abnormality represents limitation of standard techniques rather than vascular health.

This phenomenon is by no means restricted to Crohn's disease and occurs in probably all forms of inflammatory bowel disease. Early anatomical studies of allograft rejection showed peripheral macrophage accumulation with vasculopathy, and severe acute vasculopathy has been found in a class II MHC restricted model of renal allograft rejection. Neovascularisation clearly must also occur, and it is clear from embryological studies that macrophages may induce this: TNFα itself may contribute to new vessel formation as well as to the initial vasculopathy. In this case, the ability to remodel tissue with production of appropriately normal extracellular matrix, rather than collagen, will determine outcome. The role of TNFα in the control of fibroblast function may thus be of greater importance than is currently recognised.

S H MURCH
Department of Paediatric Gastroenterology, St Bartholomew's Hospital, London EC1A 7BE


**Mycobacteria in the human intestine**

**EDITOR—**We read with much interest the article by Stainsby et al (Gut 1993; 34: 371-4) about antibodies to mycobacteria in Crohn's disease and control subjects. They showed that a spectrum of antibodies binding to tuberculobacteria species was evident in control as well as patient populations, reflecting the ubiquitous nature of mycobacteria in the environment.

We also confirmed the ubiquitous nature of mycobacteria in the human intestine, detected by polymerase chain reaction (PCR). The DNA extracted from the colonic tissues from patients with Crohn's disease, ulcerative colitis, and controls were amplified by PCR using TB1 and TB2 as primers to amplify the mycobacterial groEL gene. Mycobacteria were detected in seven of 10 inflammatory bowel disease patients (3/5 with Crohn's disease and 4/5 with ulcerative colitis). Four of five control tissues were also positive for mycobacteria. These results suggested that some kinds of mycobacteria may be ubiquitously distributed in the human intestine or
much,2,3 several comprehensive associations inCrohn'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. tuberculosis* in Crohn's disease should be devoid of the cross reactive nature of mycobacterial antigens. Furthermore, Sanderson et al reported that *M. tuberculosis* DNA was identified in the mucosa of active Crohn's disease, in 23 of 43 (43%) 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. tuberculosis* in Crohn's disease could not be explained by secondary invasion of a previously damaged mucosa. Therefore, some kind of mycobacteria may be ubiquitously distributed in the human intestine, but *M. tuberculosis* might participate in the pathogenesis of Crohn's disease.

YOKOYAMA J KING K OKAZAKI Y YAMAMOTO
First Department of Internal Medicine, Kochi Medical School, Nankoku, Kochi, Japan


**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, and involved the comparison of geographically and ethnically disparate populations, so subgroup analysis for risk factors in *H pylori* infection may not be appropriate.

It is possible that *H pylori* serology does not always correlate well with active infection in apparently healthy subjects, and may merely provide a historical record.3

The 17 groups studied between 1983 and 1988 were each population from 1 of 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.4 For the current cigarette smokers there was a clearly increased prevalence of *H pylori* infection (49-6% vs 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 continuously very strongly ulcer 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 provide a similarly coherent specific study devoted to this problem.

M C BATESON
Bishop Auckland General Hospital, Bishop Auckland, County Durham DL14 6AD

**1 EUROGAST Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993; 341: 1359-62.**


**3 EUROGAST Study Group. Epidemiology of, and risk factors for *Helicobacter pylori* infection among 3194 asymptomatic subjects in 17 populations. Gut 1993; 34: 1672-6.**


**5 Bateson MC. Cigarette smoking and *Helicobacter pylori* infection. Postgrad Med J 1993; 69: 41-4.**

**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 from different centres 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. 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 the factors for *H pylori* infection.

The lack of association between *H pylori* and smoking was seen in the whole *EUROGAST* population1 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 vs non-smokers was 1·0 or higher in 10 out of 17 study centres and was lower than 1·0 in 2 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, as assessed by serology,2 by serology and the urea breath test,3 and by serology and histology.4 The last two studies4 used measures of current infection in addition to serology. Moreover, there is evidence suggesting that *H pylori* infection is most commonly acquired in early childhood5-6,7—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,8,9 negative10 or no11 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 aetiological relation. Rather, it is plausible that smoking may increase the risk of disease in an *H pylori* infected subject.15 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 occur in healthy subjects who did not become infected 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 recent infection, those who have been infected in the past, 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.

P WEBB D MURPHY
H MOLLER
F NEWELL
(on behalf of the *EUROGAST* Study Group)
Imperial Cancer Research Fund Cancer Epidemiology Unit, University of Oxford, Gibson Building, The Headington, Oxford OX2 8EJ

**1 EUROGAST Study Group. Epidemiology of, and risk factors for, *Helicobacter pylori* infection among 3194 asymptomatic persons in 17 countries. Gut 1993; 34: 1672-6.**


**7 Detterman M, Nyst JF, Jonas C, Chlupaucky Y, Depret C, Buretta A. Clinical, endoscopic and histologic findings in 1100 patients of whom 574 were colonized by *Campylobacter pylori*. Gastroentrol Clin Biol 1989; 13: 89-95.**

**8 Arenberg DZ, Rudasky B, Dollberg L, Morrisal GA, Patz JK, Jacobin M, et al. Campylo-