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.[1] 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 gastric secretion 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.[2] In fact, all patients receiving gastric secretion inhibitors had manometrically proved impaired oesophageal motility and abnormal gastro-oesophageal reflux 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%.[1]

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 candidosis in any of their patients.[2] Eradication of candidal growth by nystatin or fluconazole did not influence the severity of oesophagitis,[1 2] and did not further relieve reflux symptoms previously improved by anti-reflux treatment.[2] On the other hand, gastric mucosal erosions and an increase in serum alkaline phosphatase were seen after fluconazole treatment.[2]

Patients with systemic sclerosis, impaired oesophageal peristalsis, and oesophagitis 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[3] 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 part played by *Candida albicans* in oesophagitis 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 usefulness of antimycotic treatments in patients with systemic sclerosis should be defined by appropriate controlled trials.

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Tumour necrosis factor α in inflammatory bowel disease

EDITOR,—Murch *et al* (*Gut* 1993; **34:** 1705–9) show beautifully 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 what is illustrated by the figures. Nevertheless, their assertion that there is periarteriolar infiltration by TNF positive cells ('vasculopathy') may be true. In their discussion they review much evidence for why this could 'contribute 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.

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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 pathogenetic mechanisms 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 elegant perfusion-fixation study[1]: 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 abnormality has long been 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,[2] and we have additionally shown widespread attenuation of endothelial heparan sulphate in apparently healthy vessels.[3] 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 cell mediated immunopathologies. Early anatomical studies of allograft rejection showed perivascular macrophage accumulation with vasculopathy,[4] and severe acute vasculopathy has been found in a class II MHC restricted model of renal allograft rejection.[5]

Neovascularisation clearly must also occur, and it is clear from embryological studies that macrophages may induce this[6]: TNFα itself may contribute to new vessel formation as well as to the initial vasculopathy.[7] In this case, the ability to remodel tissue with production of appropriately normal extracellular matrix, rather than collagen, will determine outcome. The role of cytokines such as TNFα in the control of fibroblast function may thus be of greater importance than is currently recognised.

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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 mycobacterial 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 by polymerase chain reaction (PCR). The DNA extracted from the colonic tissues from patients with Crohn's disease, ulcerative colitis, and controls were subjected to PCR using TB1 and TB2 as primers to amplify the mycobacterial *groEL* gene.[1] 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