Cytokine production in inflammatory bowel disease

**EDITOR,—We read with considerable interest both the paper by Dr Mazlam and Professor Hodgson concerning cytokine production in inflammatory bowel disease (**Gut** 1994; 35: 77–83), and the accompanying leading article. A number of points emerge that are worth of further discussion.

There are many practical difficulties in attempting to compare, quantitatively, the acute phase response in Crohn’s disease with the response in ulcerative colitis. In particular, it is critically important to match patient groups precisely for disease activity, extent, and drug treatment before drawing any conclusions. Comparing differences in monocyte cytokine production in Crohn’s disease and ulcerative colitis.

Mazlam and Hodgson have used clinical indices of disease activity only, and provide no details of histology or endoscopic appearances. These clinical indices are subject to considerable criticism, and reappraisal. Moreover, in the patient group described as having ‘active’ ulcerative colitis, seven had mildly and four had actively active disease. No patients with symptoms of severe active colitis — those most likely to have an acute phase response, and systemic illness — were included. Therefore, we would suggest that there is not sufficient information to draw any valid conclusions regarding cytokine production in acute inflammatory bowel disease.

In their study, most patients with ulcerative colitis, had limited distal disease. Only one of 22 patients had total colonic involvement. It is not only our clinical experience but also well reported1 by other authors that patients with proctitis or distal ulcerative colitis may fail to display an acute phase response, as assessed by C-reactive protein and monocyte or erythrocyte sedimentation rate. Normal values may occur, even in patients with symptoms of severe acute colitis.

Mazlam and Hodgson have themselves recently shown the effects of **5ASA drugs** on cytokine production by peripheral blood monocytes.3 Other workers have described4 an inhibitory effect of sulphasalazine and **5ASA** on the actions of tumour necrosis factor. This important aspect, however, is not discussed in their paper. We would like to know whether corticosteroid treated patients had active disease at the time of venesection, and the relation between corticosteroid and monocyte cytokine production, for individual patients.

Although previous studies (including our own early findings5) have suggested differences in cytokine production by peripheral blood mononuclear cells in ulcerative colitis and Crohn’s disease, we continue to have reservations. There remains a need for a further study, using well matched groups of patients with active disease. Studies of mucosal cytokine production in such patients are also needed.

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Replication

**EDITOR,—Satsangi and Jewell raise a considerable number of points relevant to the immunological aspects of inflammatory bowel disease, which though well recognised by workers in the field perhaps merit a general airing.

Any investigation of immunological aspects of inflammatory bowel disease must indeed attempt to describe as far as possible the extent, duration, and activity of the inflammatory process at the time. We have considered this topic in its own right in a recent review.2 We have given the following provided simultaneous histological and endoscopic assessment of all our patients at the time peripheral blood was taken for assessment of cytokine activity — although in the 14 Crohn’s patients who had ileal involvement or ileocolitis this had presented formidable difficulties; more seriously, we worry that Satsangi and Jewell are taking us to task for not accurately matching patients with Crohn’s disease with patients with ulcerative colitis. That is clearly impossible, given the differences in distribution of inflammation in patients in whom a firm clinical distinction can be made. If we match two patients with similar degrees of continuous inflammation and limited to the mucosa extending for a similar distance proximally from the rectum, we may have difficulty persuading the reviewers we are comparing ulcerative colitis and Crohn’s disease!

With respect to drug treatment: in preparing the paper we assessed whether or not the use of anti-inflammatory drugs could explain the differences in cytokine production either between patients with inflammatory bowel disease when active and inactive, or between ulcerative colitis and Crohn’s patients with similar disease activity. Clearly, as in most published studies in inflammatory bowel disease, the patient cohorts become small (that is, subgroup – ulcerative colitis, inflammation active, distribution left sided, corticosteroid treatment – local yes, systemic no, salazopyrine treated),3, 1988; 23: 1119. Indeed, on that level neither of the uses of corticosteroids or aminosalicylates as treatment abolished cytokine generation, or explained the differences noted. Incidentally, the correspondents’ own work has shown the ability of mononuclear cells from inflamed inflammatory bowel disease tissue to continue to produce abnormally high amounts of cytokines despite corticosteroid treatment.2

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Oesophageal acid clearance

**EDITOR,—The report of reduced oesophageal acid clearance in patients with progressive systemic sclerosis by Basillo et al. (**Gut** 1993; 34: 1487–91), reflecting the disordered oesophageal motility in this condition, may prompt clinicians to use more potent gastric acid inhibitory treatment for oesophagitis in such patients. Such a policy, however, might not be without hazard, particularly with respect to the frequency of oesophageal candidal infection.

Hendel et al found Candida albicans in oesophageal mucosal brushings from 44% of systemic sclerosis patients, but in a subgroup of patients treated with either high dose ranitidine (more than 300 mg/day) or omeprazole (40 mg/day) for oesophagitis, the frequency rose to 89%.1 Hence, oesophageal dysmotility predisposes to candidiasis but inhibition of gastric acid secretion significantly enhances the risk. On the basis of such results and other reports of candidiasis complicating therapeutic interventions producing hypoaacidity, it has been suggested2 that physiological gastro-oesophageal acid reflux is a non-specific protective action against oesophageal candidiasis, and that diminution or abolition of acid reflux by agents such as H2 receptor antagonists or omeprazole may exacerbate the risk of developing oesophageal candidiasis, particularly in patients with impaired oesophageal motility. These considerations suggest that, notwithstanding their impaired oesophageal acid clearance, potent inhibitors of gastric acid secretion such as omeprazole should be prescribed with caution in patients with systemic sclerosis,1 or in conjunction with prophylactic anti-candidal treatment such as nystatin or, preferably, fluconazole.

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Letters
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 with out 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 ero-

sive oesophagitis and oesophageal strictures. Thus, impaired oesophageal peristalsis, oeso-

phagitis or oesophageal strictures may favour fungal growth in patients with systemic sclero-

sis. If this hypothesis is true, the increased freq-

quency of positive cultures for Candida albicans reported by Hendel et al in their subgroup of systemic sclerosis patients treated with gastric acid inhibition may reflect not only from the effect of treatments but also from the higher frequency of severe oesophageal involvement in this group of patients in comp-

arison with our patients. 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%.

Whatever the case 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 pre-

viously present in patients treated with 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 motility and oesophageal reflux symptoms that are often severe, and oeso-

phageal 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 marked decrease in 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 effectiveness of microvas-
cotic treatments in patients with systemic sclerosis should be defined by appropriate controlled trials.


2 Hendel L, Sveigaard E, Walloe I, Kieffer M, Stenndrup A. Esophageal candidiasis in progres-


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

**EDITOR,—**Murch et al ( Gut 1993; 34: 1705-9) show beautifully that tumour necro-

sis factor (TNF) containing cells, probably macrophages, are clustered in the upper 
mucosa in ulcerative colitis and are dis-

tributed more randomly, and apparently diffusely, in Crohn’s disease. Unfortunately, the legends to their colour figures do not match with their text. Nevertheless, their assertion that there is periarterial infiltration by TNF positive cells ('vasculopathy') may be true. In their discussion they review much evidence for why this could be deleteriously 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 the 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 perfusion-fixation study: 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 endo-

scopic biopsy specimens. While vascular abnormalities have been identified in Crohn’s disease, it is probable that only size-

able vessels will lose 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 microscopic abnormality repre-

sents limitation of standard techniques rather than vascular health.

This phenomenon is by no means re-

stricted to Crohn’s disease and occurs in prob-

ably all inflammatory bowel disease.

Early anatomical studies of allograft rejection showed perivascular macrophage accumula-

tion 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: TNFs itself may contribute to new vessel formation as well as to the initial vasculopathy. In this case, the ability to remodel tissue with produc-

tion of appropriately normal extracellular matrix, rather than collagen, will determine outcome. The role of TNFs in the control of fibroblast function may thus be of greater importance than is currently recognised.

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5 Duizerijn AM, van Breda Vriesman PJ. Chronic renal allograft rejection. Selective involvement of the glomerular endothelium in humoral immune reactivity and intravascular coagula-


**Mycobacteria in the human intestine**

**EDITOR,—**We read with much interest the article by Stainbsy 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 different 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 human intestine, detected by poly-

merase 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 *proEL* 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 ubiqui-

tously distributed in the human intestine or

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