LETTERS TO THE EDITOR

Cytokine production in inflammatory bowel disease

EDITOR,—We read with considerable interest both the paper from 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 worthy 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 regarding 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 moderately 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 reported[1 2] 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 concentration 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 corticosteroids (and 5ASA drugs) on cytokine production by peripheral blood monocytes.[3] Other workers have described[4] 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 drug treatment and monocyte cytokine production, for individual patients.

Although previous studies (including our own early findings[5]) 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.

J SATSANGI
D P JEWELL
Gastroenterology Unit,
The Radcliffe Infirmary,
Oxford OX2 6HE

1 Prantera C, Davoli M, Lorenzetti R, Palone F, Macheggiano A, Iannoni C, *et al.* Clinical and laboratory indicators of extent of ulcerative colitis – serum C-reactive protein helps the most. *J Clin Gastroenterol* 1980; **10:** 41–5.
2 Tromm A, Hüppe D, Eckenberg K, Schwegler U, Krieg M, May B. Laboratory tests and activity indices in acute ulcerative colitis with respect to the extent of disease. *Eur J Gastroenterol Hepatol* 1993; **5:** 21–6.
3 Mazlam MA, Montazeri G, Hodgson HJF. The effects of some anti-inflammatory agents on cytokine release from human monocytes in vitro. *Eur J Gastroenterol Hepatol* 1993; **5:** 515–21.
4 Greenfield SM, Hamblin AS, Shakoor ZS, Teare JP, Punchard NA, Thompson RPH. Inhibition of leucocyte adhesion molecule upregulation by tumour necrosis factor α: a novel mechanism of action of sulphasalazine. *Gut* 1993; **34:** 252–6.
5 Satsangi J, Wolstencroft DC, Ainley CC, Wolstencroft RA, Dumonde DC, Thompson RPH. Interleukin-1 in Crohn's disease. *Clin Exp Immunol* 1987; **67:** 594–605.

Reply

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

Any investigation of immunological aspects of inflammatory bowel disease must indeed attempt to describe as far as possible the extent, distribution, and activity of the inflammatory process at the time. We have considered this topic in its own right in a recent review.[1] We plead guilty to not having 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 would have 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 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 one type of 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, numbers become small (that is, subgroup – ulcerative colitis, inflammation active, distribution left sided, corticosteroid treatment – local yes, systemic no, salazopyrine treated), and the analysis is therefore impressionistic. On that level neither the use 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]

We look forward to the correspondents' next contribution in this field, and hope it may resolve both their and our reservations.

H J F HODGSON
M Z MASLAM
Gastroenterology Unit,
Department of Medicine,
Royal Postgraduate Medical School,
Hammersmith Hospital,
Du Cane Road,
London W12 0NN

1 Hodgson HJF, Maslam MZ. Assessment of disease activity in inflammatory bowel disease. *Alim Pharmacol Therap* 1991; **5:** 555–84.
2 Mahida YR, Wu K, Jewell DP. Enhanced production of interleukin 1-β by mononuclear cells isolated from mucosa with active colitis or Crohn's disease. *Gut* 1989; **30:** 835–8.

Oesophageal acid clearance

EDITOR,—The report of reduced oesophageal acid clearance in patients with progressive systemic sclerosis by Basilico *et al* (*Gut* 1993; **34:** 1487–91), reflecting the disordered oesophageal motility in this condition, might 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 candidosis 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 hypoacidity, it has been suggested[2] that physiological gastro-oesophageal acid reflux may have a protective action against oesophageal candidiasis, and that diminution or abolition of acid reflux by agents such as H_2 receptor antagonists or omeprazole may exacerbate the risk of developing oesophageal candidiasis, most 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.

A J LARNER
Department of Anatomy,
University of Cambridge,
Downing Street,
Cambridge CB2 3DY

1 Hendel L, Svejgaard E, Walsoe I, Kieffer M, Stenderup A. Esophageal candidosis in progressive systemic sclerosis: occurrence, significance, and treatment with fluconazole. *Scand J Gastroenterol* 1988; **23:** 1182–6.
2 Larner AJ, Lendrum R. Oesophageal candidiasis after omeprazole therapy. *Gut* 1992; **33:** 860–1.

Reply

EDITOR,—Larner's letter raises the issue that gastric acid inhibition may increase the frequency of oesophageal candidal infection in patients with systemic sclerosis, and suggests