LETTERS TO THE EDITOR

Soluble TNF receptors as prognostic factors for mortality

EDITOR,—We read with interest the paper by Bemelmans *et al* (*Gut* 1996; **38:** 447–53) describing their investigations of systemic tumour necrosis factor (TNF) and soluble TNF receptor (sTNFr) concentrations in mice with biliary obstruction. Endotoxaemia has been demonstrated frequently in both clinical and experimental biliary obstruction. It is probably responsible for much of the morbidity and mortality seen in jaundiced patients[1] and exerts these effects by stimulating the release of cytokines – for example, TNF. We have previously reported increased TNF secretion by Kupffer cells[2] and peritoneal macrophages[3] in jaundiced rats, and Puntis and Jiang have described increased TNF secretion from stimulated peripheral blood monocytes in jaundiced patients.[4] Soluble TNF receptors are released during Gram negative sepsis and in response to endotoxin and TNF.[5 6] The findings of Bemelmans and colleagues, of increased systemic concentrations of both TNF and sTNFr in mice with biliary obstruction, support the hypothesis suggesting that TNF is an important mediator in the systemic inflammatory response to endotoxin in the jaundiced host.

Bemelmans *et al* found that systemic TNF and sTNFr concentrations were increased further following surgical trauma and that only sTNFr concentrations correlated with subsequent mortality. These results suggest that the sTNFr concentration may be a better indicator of ongoing inflammation and a more accurate predictor of outcome than TNF. In patients with inflammatory bowel disease[7] and acute pancreatitis,[8] plasma sTNFr concentrations correlate better with disease activity than measurements of TNF. Soluble TNF receptor concentrations were increased in patients with rheumatoid arthritis and osteomyelitis in the absence of detectable TNF.[9] This difference between TNF and sTNFr may result from the longer plasma half life of sTNFr and biological inactivation of some detectable systemic TNF.

On the basis of this evidence it was reasonable to expect that administration of TNF antibody would improve outcome in animals with biliary obstruction undergoing surgery. The reason for the failure of TNF antibody treatment to reduce systemic sTNFr concentration or mortality, despite reducing TNF concentrations, is unclear. The results were derived from blood samples taken eight and a half hours after administration of TNF antibody, and it is possible that further samples at 31 hours or later would have shown a reduction in the sTNFr concentrations. It is interesting that TNF antibody administration has recently been shown to reduce disease activity in patients with inflammatory bowel disease in an uncontrolled study[10] and in a randomised controlled trial.[11] Clearly, further study of sTNFr and the use of anti-TNF antibody in clinical and experimental obstructive jaundice is indicated to elucidate the relation among clinical features, cytokine activation and therapeutic intervention.

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Reply

EDITOR,—We thank Dr Parks and colleagues for their interesting comments on our article on TNF and sTNFr in biliary obstruction. We agree that sTNFr concentrations are better indicators of the inflammatory response than TNF in several diseases such as pancreatitis and Crohn's disease. Nevertheless, more information on TNF and its release and function could also offer new insights and possibly more strategies for treating patients.[1]

Concerning their question on sTNFr concentrations 24 hours after induction of renal ischaemia, we can say that there was a tendency towards lower sTNFr concentrations in all surviving mice after 24 hours, although these concentrations were still relatively high. The kinetics of the sTNFr concentrations differed strongly from the endotoxin induced sTNFr increase, where peak levels of sTNFr-P55 were found at 30 min and peak levels of sTNFr-P75 four to eight hours after LPS injection.[2] There was no specific decline in sTNFr concentrations in the TN3 group as suggested by Dr Parks, although one has to say that the number of mice in all groups was to small to draw definite conclusions. Additional experiments with more mice which will be followed over a longer time interval after induction of renal ischaemia will be necessary to answer their questions completely.

Finally, we agree with their concluding remark on the importance of further research in obstructive jaundice and the cytokine cascade in this disease.

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Helicobacter pylori and ulcer healing

EDITOR,—Bianchi Porro *et al* (*Gut* 1996; **39:** 22–6) conclude that eradication of *Helicobacter pylori* does not confer any significant advantage on the healing of gastric and duodenal ulcers associated with long term use of non-steroidal anti-inflammatory drugs (NSAIDs). It is questionable, however, whether they have truly shown this in their study.

In the study, *H pylori* positive patients with NSAID related peptic ulcers were randomised to treatment with either omeprazole plus amoxycillin or omeprazole alone. Although it is not stated, it might be assumed that characteristics such as age, sex, smoking status, and dose and nature of the NSAID ingested were similar in both treatment groups. Of the 36 subjects who received omeprazole and amoxycillin, only 20 (56%) were cleared of *H pylori* infection. Comparing the healing rates in only these 20 subjects with the rates in those where *H pylori* persisted defeats the purpose of the original randomisation and raises the possibility that confounding factors explain the failure to observe a difference in healing rates.

Analysing the results on an intention to treat basis would allow a conclusion to be made as to whether attempting to treat *H pylori* positive subjects with omeprazole and amoxycillin is associated with a difference in ulcer healing rate. An intention to treat analysis would not, however, permit a conclusion to be made regarding the effect of *H pylori* eradication given that eradication was only successful in 56% of patients.

Similarly, the analyses of ulcer recurrence rates need to be interpreted with caution given that it is unclear whether the groups involved were matched for confounding factors, such as those listed above, which have been reported to be risk factors for NSAID related peptic ulcer disease.[1 2]