LETTERS TO THE EDITOR

Soluble TNF receptors as prognostic factors for mortality

EDITOR,—We read with interest the paper by Benemlans et al (Gut 1996; 38: 560-563) describing their investigations of systemic tumour necrosis factor (TNF) and soluble TNF receptor (sTNFr) concentrations in mice with biliary obstruction. Endotoxemia 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 and exerts these effects by stimulating the release of TNF by Kupffer cells and peritoneal macrophages in jaundiced rats, and Puntis and Jiang have described increased TNF secretion from stimulated peripheral TNF monocytes in jaundiced patients. Soluble TNF receptors are released during Gram-negative sepsis and in response to endotoxin and TNF. The findings of Benemlans and colleagues showed increased systemic TNF and sTNFr concentrations in 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 animal.

Benemlans 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 and acute pancreatitis, plasma TNF concentrations correlated better with disease activity than measurements of TNF. Soluble TNF receptor concentrations were increased in patients with rheumatoid arthritis, chronic osteomyelitis and osteomyelitis in the absence of detectable TNF.

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. We have found that TNF antibody administration to reduce systemic TNF 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 the 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 and in a randomized controlled trial. 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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Replies

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 amoxicillin or omeprazole alone. Although it is not clear why, it might be assumed that characteristics such as sex, age, smoking status, and dose and nature of the NSAID ingested were similar in both treatment groups. Of the 36 subjects who received omeprazole and amoxicillin, 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 destroys 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 treatment with H pylori positive subjects with omeprazole and amoxicillin is associated with a difference in ulcer healing rate. An intention to treat analysis would not, however, permit any conclusions 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.