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: 58-63) 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 and exerts these effects by stimulating a range of pro-inflammatory cytokines, including TNF. We have previously reported increased TNF secretion by Kupffer cells and peritoneal macrophages in jaundiced rats, and Punth 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 Bemelmans and colleagues of 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 animal.

Bemelmans et al found that systemic TNF and sTNFr concentrations were increased 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 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. 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. However, the results of this study suggest that the use of an anti-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 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 relationship among clinical features, cytokine activation and therapeutic intervention.

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6 Van Zee WG, Bemelmans VWM, Puntis I, Kirk WA. Monocytes from mice undergoing an inflammatory response behave as acute phase reactants following surgery in mice with adenoma and coeliac disease. GUT 1995; 36: 897-901.

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 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 amoxicillin, only 20 (56%) had H pylori eradicated. 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 H pylori positive patients with or without NSAID use are cleared of H pylori infection. Comparing the healing rates in only the 20 subjects with the rates in those where H pylori persisted would not, however, permit 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.

2 Bemelmans MHA, Gouma DJ, Buurman WA. LPS induced sTNF-receptor expression is not influenced by a murine model: investigation of the role of TNF, IFN-1, IFN-γ and TNF-α. Immunol 1995; 131: 5544-62.

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Letters, Book reviews

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Reply

Editor,—Dr Dowling is right to emphasise that the eradication rate we obtained in our *H pylori* positive, NSAID associated peptic ulcers is fairly low (56%), and more convincing conclusions could have been made by using a more effective eradicating regimen (that is, omeprazole based triple therapy) providing a cure rate of at least 85-90%. Unfortunately, when this clinical study was originally planned (spring 1993), dual therapy (omeprazole with amoxicillin) was considered one of the most effective eradicating regimens available; however, it should be emphasised that the *H pylori* cure rate obtained with omeprazole/amoxicillin in this series is comparable with that reported previously in NSAID unrelated peptic ulcers using the same combination of drugs.1 2 We also agree on the fact that our results should be considered preliminary because of the limited number of NSAID associated ulcers treated, and they need to be confirmed in further clinical trials involving larger series of patients on long term NSAID treatment with gastric or duodenal, or both, ulcer disease.

However, two important points emerge from our study. First, unlike NSAID unrelated peptic ulcers, eradication of *H pylori* is not associated with the “cure” of NSAID associated ulcers which tend to recur rapidly after initial healing if the patient continues to receive the NSAID but stops taking antieulcer medication. This necessarily implies that the risk is not reduced by the presence of *H pylori* infection, if any, as small and it is only additional to the main risk of receiving long term NSAID treatment. Second, *H pylori* status does not seem to have an important role in the healing of these lesions. This is not only confirmed by the observation that the rate of healing is not increased by eradication of *H pylori*, but also from the fact that *H pylori* negative ulcers respond to omeprazole just as well as *H pylori* positive ones. The major determinant of healing response to the anti-secretory compound in these patients seems to be the concomitant intake of the NSAID during the healing phase, which delays the healing process irrespective of the type of drug used.

Recently, Hawkey et al,3 in a very large study involving 541 patients with NSAID related gastroduodenal ulcers or erosions, have shown that coinfection with *H pylori* does not hamper the healing efficacy of omeprazole 20-40 mg daily; on the contrary, it tends to be associated with higher healing rates, perhaps as a result of the increased antisecretory effects of proton pump inhibitors in this setting.4

1 Tytgat GNJ, van der Hulst RWM. Important acquisition in Helicobacter pylori infection. Curr Opin Gastroenterol 1996; 11 (suppl 1): 57-60.

Endoscopic papillotomy

Editor,—I read the recent article on endoscopic papillotomy by Dr Farrell et al (Gut 1996; 39: 36-8) with considerable interest because of a simple experiment done in 1964, which indicates that papillotomy might be hazardous.1 The closed duodenal loop model of haemorrhagic necrotic pancreatitis closely resembles severe human pancreatitis and is caused by the reflux of duodenal contents through the papilla of Vater; it was suggested that pancreatitis could be produced by much smaller intraduodenal pressures provided that the papilla of Vater was damaged in incompetent.

The duodenal papilla in humans and in dogs is lined by mucosal folds or 'valvules', which serve to prevent regurgitation of duodenal contents.1 2 The isolated dog duodenum was filled with coloured saline maintained at a pressure of 30 mm Hg without any fluid escaping from the cut ends of the pancreatic ducts or common bile duct. A simple mucosal papillotomy was performed at the main pancreatic duct and duodenal orifice. The common bile duct was closed, and the intraduodenal pressure raised again to 30 mm Hg. Within two minutes coloured saline oozed from the main pancreatic duct but not from the separate lesser pancreatic duct and the common bile duct. When the common bile duct papilla was also excised saline escaped from the common bile duct.1 The histological picture of the papilla, before and after excision (photographed), plus the findings above suggest that: (1) the mucosal portion of the papilla of Vater serves a useful purpose in preventing duodenal reflux; (2) papillotomy may increase the risk of developing pancreatitis, depending on the nature of the underlying pathology for which papillotomy was performed.

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A review of the second edition of this book published in 1995 was only requested in late 1996 (accompanied by an invoice marked “rush!”) which explains the interval between publication and this review.

I was brought up on Gray’s Anatomy to achieve adult height around the dining table. A wide selection of two volume books on gastroenterology could now do this job admirably.

This remarkable book has more than 200 contributors, mostly North American with a smattering of other contributors from seven different countries. Its approach is so different that comparison with other textbooks of gastroenterology is inappropriate. No other book could find the reviewer at the end of volume one, some 67 chapters and 1500 pages later, still not yet through the pylorus. This is not an obsession with the oesophagus and stomach, but extensive consideration of basic mechanisms relevant to clinical problems (26 chapters) and, more importantly, an extended section of similar length concerned with approaches to the symptomatic patient. This section is particularly relevant for the younger postgraduate whose patients in real life present with a constellation of symptoms rather than a specific diagnosis. This focused approach is both a strength and a weakness as...