Gut, 1990, **31**, 938-939

HYPOTHESIS

Tumour necrosis factor, cholestatic jaundice, and chronic liver disease

A Jones, P J Selby, C Viner, S Hobbs, M E Gore, T J McElwain

DNA recombinant technology provides us with large quantities of pure biologically active materials for scientific and clinical evaluation. It seems likely that studies evaluating their treatment value will also yield insights into the biological processes which they control.

Tumour necrosis factor is a protein released by activated macrophages in response to stimulation by endotoxin. Its characteristic effect is to produce necrosis of experimental mouse tumours.[1] It has diverse biological effects in other biological systems, however, including in vitro tumour cell killing,[2] inhibition of lipoprotein lipase,[3] mediation of endotoxin effects,[4] stimulation of granulocytes and fibroblasts,[2 3 5] damage to endothelial cells,[6] bone resorption,[7] antiviral activity,[8] and antimalarial actions.[9 10] Macrophage tumour necrosis factor should now be called tumour necrosis factor α and the term tumour necrosis factor β is used for lymphotoxin, a closely related lymphocyte product.[11]

The gene for human tumour necrosis factor has now been expressed in *Escherichia coli* and large quantities of human recombinant tumour necrosis factor are available for experimental and clinical evaluation.[11-14] Recombitant tumour necrosis factor contains 155 amino acids and is usually arranged in multimeric form. Initially, a propeptide is synthesised, and both precursor and protein are about 80% conserved between mouse and man.[2 3 11 12 14 15] The gene in man is found on chromosome 6.[16] Tumour necrosis factor interacts with high affinity receptors,[17 18] although its anti-cancer effect could be mediated indirectly, perhaps via endothelial cell damage.

In our initial study of exogenous tumour necrosis factor administered as a potential anti-cancer agent,[19] we noted abnormal liver enzymes, particularly alkaline phosphatase, as adverse reactions (Table) and this has been confirmed by others.[20] Transient hyperbilirubinaemia was seen in three of 12 patients (bilirubin <100 μmol/l). In a subsequent patient we saw frank cholestatic jaundice after exogenous tumour necrosis factor at a dose of 6×10^5 U/month. This patient developed a transient cholestatic jaundice on two occasions, each following a dose of tumour necrosis factor, as shown in the Figure. The hyperbilirubinaemia consisted almost entirely of conjugated bilirubin and was associated with an increase in alkaline phosphatase activity on each occasion. Although liver ultrasound was abnormal with probable tumour infiltration, the changes in liver function coincided with tumour necrosis factor administration and were reversible, making tumour necrosis factor the likely aetiology for hepatic dysfunction. The gamma glumatyl transpeptidase activity was a particularly sensitive variable, with two to six fold increases per drug course. No new drugs, apart from ketoprofen to obviate rigors caused by tumour necrosis factor, were introduced during the study. Liver biopsies were not performed in these patients for ethical reasons.

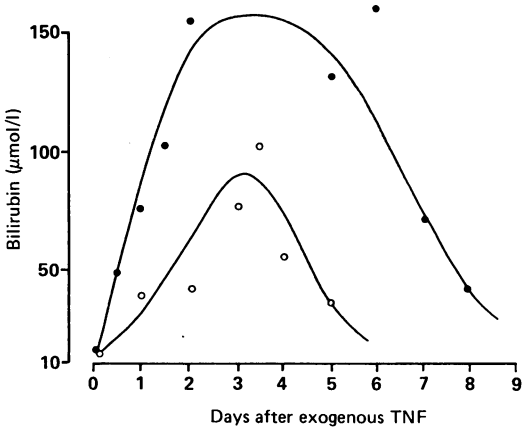
Muto *et al*[21] have observed increased production of tumour necrosis factor by mononuclear cells in short term culture from patients with fulminant hepatic failure. They point out that tumour necrosis factor and interleukin 1 may be produced by mononuclear cells in hepatic failure as a result of bacterial or fungal infection and that the cytokines may contribute to liver cell necrosis.

These observations suggest the hypothesis that tumour necrosis factor has a direct patho-

Deterioration in hepatic function in relation to tumour necrosis factor (TNF)

	Patients with abnormal value before treatment	*Patients with deterioration* in parameter after TNF*
Bilirubin	0/12	3/12
Alkaline phosphatase	8/12	11/12
Alanine transaminase	2/12	7/12
Gamma glutamyl transpeptidase†	5/9	9/9

*Deterioration assessed by WHO criteria.[22]
†Gamma glutamyl transaminase was not measured in all patients as baseline.



Changes in serum bilirubin concentration after intravenous recombinant human tumour necrosis factor (TNF).

Section of Medicine, Royal Marsden Hospital, Sutton, Surrey
A Jones
P J Selby
C Viner
S Hobbs
M E Gore
T J McElwain

Correspondence to:
Prof P J Selby, Institute for Cancer Studies, Clinical Sciences Building, Level 05, St James's University Hospital, Beckett Street, Leeds LS9 7TJ.

Accepted for publication 24 October 1989

genetic role in abnormalities of liver function and in cholestasis. Furthermore, we would suggest that it is possible that local or systemic production of tumour necrosis factor by mononuclear cells may contribute to cholestasis not only in acute fulminant hepatic failure and septicaemia but also in chronic liver diseases. In primary biliary cirrhosis, for instance, granulomatous infiltration is commonly seen near bile ducts and the mononuclear cells may be producing high local concentrations of tumour necrosis factor. Tumour necrosis factor is produced in response to both RNA and DNA viruses.[15] Could it be implicated in post viral cholestasis? The investigation of localised and generalised tumour necrosis factor production is appropriate in chronic hepatic disorders where cholestasis is a feature. We are performing experiments in a number of model systems but clinically related work could be done by hepatologists.

1 Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson BD. An endotoxin-induced serum factor that causes necrosis of tumours. *Proc Nat Acad Sci* 1975; **72:** 3666–70.
2 Old LJ. Tumour necrosis factor (TNF). *Science* 1985; **230:** 630–2.
3 Beutler B, Cerami A. Cachectin: more than just a tumour necrosis factor. *New Engl J Med* 1987; **316:** 379–85.
4 Beutler B, Milsark IW, Cerami A. Passive immunisation against cachectin/tumour necrosis factor protects mice from lethal effects of endotoxins. *Science* 1985; **229:** 869–71.
5 Vilcek J, Palombella VJ, Henriksen-de Stefano L, *et al.* Fibroblast growth enhancing activity of tumour necrosis factor and its relationship to other polypeptide growth factors. *J Exp Med* 1986; **163:** 632–43.
6 Sato N, Cioto T, Haranaka K, *et al.* Actions of tumour necrosis factor on cultured vascular endothelial cells: morphologic modulation, growth inhibition and cytotoxicity. *Nat Cancer Inst* 1986; **76:** 1113–21.
7 Bertolini DR, Nedwin GE, Bringman TS, Smith DD, Mundy GR. Stimulation of bone resporation and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986; **319:** 516–8.
8 Mestan J, Digel W, Mittnacht S, *et al.* Antiviral effects of recombinant tumour necrosis factor in vitro. *Nature* 1986; **323:** 816–8.
9 Taverne J, Dockrell HM, Playfair JHL. Endotoxin induced serum factor kills malarial parasites in vitro. *Infect Immun* 1981; **33:** 83–9.
10 Taverne J, Matthews N, Depledge P, Playfair JHL. Malarial parasites and tumour cells are killed by the same component of tumour necrosis serum. *Clin Exp Immunol* 1984; **57:** 293–300.
11 Pennica D, Nedwin GE, Hayflick JS, *et al.* Human tumour necrosis factor: precursor structure, expression and homology to lymphocytotoxin. *Nature* 1984; **312:** 724–9.
12 Shirai T, Yamaguchi H, Ho H, Todd CW, Wallace RB. Cloning and expression in *E coli* of the gene for human tumour necrosis factor. *Nature* 1985; **313:** 803–6.
13 Wang AM, Creasey AM, Ladner MB, *et al.* Molecular cloning of the complementary DNA for human tumour necrosis factor. *Science* 1985; **228:** 149–51.
14 Marmenout A, Fransen L, Tavernier J, *et al.* Molecular cloning and expression of human tumour necrosis factor and comparison with mouse tumour necrosis factor. *Eur J Biochem* 1985; **152:** 516–20.
15 Wong GHW, Goeddel DV. Tumour necrosis factors can inhibit virus replication and synergize with interferons. *Nature* 1986; **323:** 819–22.
16 Nedwin GE, Naylor SL, Sakaguchi AY, *et al.* Human lymphotoxin and tumour necrosis factor genes: structure, homology and chromosomal localisation. *Nucleic Acids Res* 1985; **13:** 6361–73.
17 Rubin BY, Anderson SL, Sullivan SA, Williamson BD, Carswell EA, Old LJ. High affinity binding of labelled human tumour necrosis factor to specific cell surface receptors. *J Exp Med* 1985; **162:** 1099–102.
18 Kull FC, Jacobs S, Cuatrecasar P. Cellular receptor for labelled human tumour necrosis factor. *Proc Nat Acad Sci USA* 1985; **82:** 5756–60.
19 Selby P, Hobbs S, Viner C, *et al.* Tumour necrosis factor in man: clinical and biological observations. *Br J Cancer* 1987; **56:** 803–8.
20 Sherman ML, Spriggs DR, Arthur KA, *et al.* Recombinant human tumour necrosis factor administered as a five-day continuous infusion in cancer patients. *J Clin Oncol* 1988; **6:** 344–50.
21 Muto Y, Ciasson J, Ogawa M, *et al.* Enhanced tumour necrosis factor and interleukin in fulminant hepatic failure. *Lancet* 1988; ii: 72–5.
22 World Health Organisation. *Handbook for reporting results of cancer treatment.* Geneva: WHO Offset Publication 48, 1979.