

HYPOTHESIS

Tumour necrosis factor, cholestatic jaundice, and chronic liver disease

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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 Recombinant 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 hyperbili-

rubinaemia was seen in three of 12 patients (bilirubin $<100 \mu\text{mol/l}$). 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 glutamyl 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-

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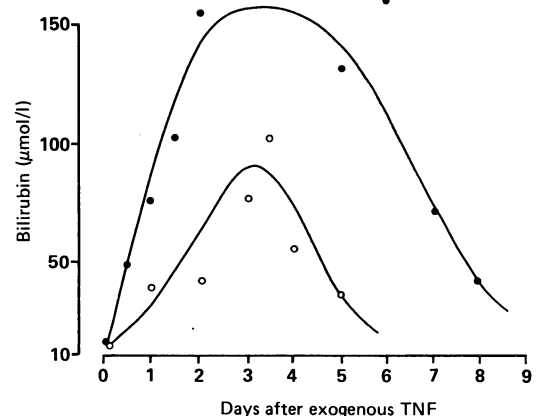
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Deterioration in hepatic function in relation to tumour necrosis factor (TNF)

| | 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).

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.

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