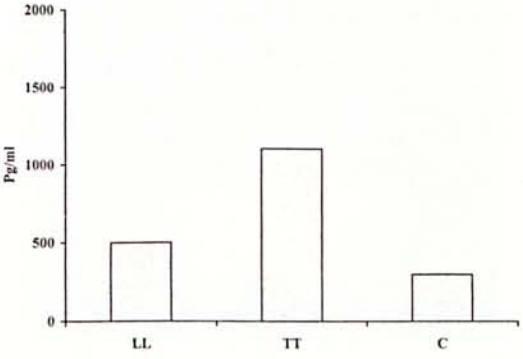
Tumor Necrosis Factor (TNF) Production in Leprosy Patients

TO THE EDITOR:

The spectrum of host response to *Mycobacterium leprae* provides a model for investigating the role of cytokines in the pathogenesis of leprosy. Of particular interest is tumor necrosis factor (TNF), a cytokine which may have both antimycobacterial and immunopathologic effects in leprosy ([2, 7]). At one pole of the leprosy spectrum, patients with tuberculoid leprosy have few skin lesions, in which bacilli can rarely be identified with strong cell-mediated immunity (CMI); at the opposite pole, patients with lepromatous leprosy have diffuse infiltration of skin and nerves with bacilli-laden macrophages and depressed CMI to *M. leprae*. To evaluate the potential role of TNF in leprosy, we measured TNF production in response to *M. leprae* in the patients with polar forms of leprosy.

Thirty-eight new patients attending the leprosy clinic at the Postgraduate Institute of Medical Education and Research, Chandigarh, India were included in the study. Patients were classified on the basis of the clinicopathologic criteria of Ridley and Jopling ([3]). Patients had not taken treatment in the past, and they were not in any reactional state. Twenty age- and sex-matched normal healthy controls were also studied simultaneously. Heparinized venous blood (7 ml) was obtained from each patient and from the controls. Plasma was separated and stored at –20°C until used, and the TNF assay was done by the method of Silva and Foss ([8]). The Student's *t* test was used to compare the control and experimental groups; values of $p > 0.05$ were considered as nonsignificant. Of the 38 patients, 25 were in the tuberculoid pole and 13 were lepromatous leprosy. TNF release was significantly higher ($p < 0.001$) in patients with tuberculoid leprosy than in those with lepromatous leprosy and healthy controls (The Figure).

TNF functions as a macrophage/monocyte-derived immunoregulatory cytokine, with important biological effects ([6]). To investigate the potential role of TNF in mediating the clinical manifestations of leprosy, we measured the production of TNF in patients from the two poles of disease. High TNF levels were demonstrated in the plasma of tuberculoid patients; however plasma levels of TNF were low in lepromatous patients and in healthy subjects. The decreased TNF production by peripheral blood mononuclear cells (PBMC) from LL patients has been attributed to an intrinsic cellular defect or deficient production of other cytokines ([1]). Decreased production of TNF in these patients may contribute significantly to the evolution of the infection.



THE FIGURE. TNF production in leprosy patients and controls. LL = lepromatous leprosy; TT = tuberculoid leprosy; C = controls.

A genetic TNF promoter polymorphism has been associated with susceptibility to diseases such as malaria, leishmaniasis, and lepromatous leprosy ([4]). In another study, TNF-alpha (TNF-α) production in healthy household contacts of newly diagnosed multibacillary (MB) patients was found to be significantly high, suggesting a role of TNF-α in restraining mycobacterial proliferation and spreading in early infection ([5]).

The wide variety of biological responses attributable to TNF, and the ability of diverse products of invasive stimuli to induce its production, suggests that TNF confers some beneficial effects to the host defense. TNF may act as an immunomodulator, capable of enhancing an antileprosy immune response by increasing the expressions of endothelial- and macrophage-activating antigens, promoting neutrophil adherence to endothelial cells, inducing IL-1 release from endothelial cells and monocytes, stimulating superoxide radical formation from neutrophils and promoting macrophage-mediated parasite killing ([9]).

TNF release appears to be triggered by the mycolylarabinogalactan-peptidoglycan complex, major cell-wall structural constituents of *M. leprae*. The prominent TNF release in patients with the tuberculoid form of leprosy compared to the lepromatous form suggest that this cytokine contributes to a resistant immune response to mycobacterial infection, but marked TNF release in patients with erythema nodosum leprosum indicates that it may also mediate the immunopathologic effects, such as fever and tissue damage. A quantitative assay of TNF production may prove to be a useful prognostic indicator of cellular immunity and subsequent course of the patient's infection.

—Inderjeet Kaur, M.D., M.N.A.M.S.

Additional Professor
Department of Dermatology, Venereology and Leprology

—Nalini Agnihotri, Ph.D.
Manjula Mehta, Ph.D.

Department of Experimental Medicine

—Sunil Dogra, M.D., D.N.B.

Department of Dermatology, Venereology and Leprology

—N. K. Ganguly, M.D.

Department of Experimental Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh 160 012, India

Reprint requests to Dr. Kaur at the above address or FAX 91-0172-744-401; e-mail: kaur_inderjeet@yahoo.com

REFERENCES

1. Abufafia, J. and Vignale, R. A. Leprosy: pathogenesis updated. Int. J. Dermatol. **38** (1999) 321–334.
2. Barner, P. F., Chatterjee, D., Brennan, P. J., Rea, T. H. and Modlin, R. L. Tumor necrosis factor production in patients with leprosy. Infect. Immun. **60** (1992) 1441–1446.
3. Jopling, W. H. and McDougall, A. C. In: *Handbook of Leprosy.* 5th edn. New Delhi: CBS Publishers, 1996, pp. 10–47.
4. Knight, J. C. and Kwaitkowski, D. Inherited variability of tumor necrosis production and susceptibility to infectious diseases. Proc. Assoc. Am. Physicians **111** (1999) 290–298.
5. Lima, M. C., Pereira, G. M., Rumjanek, F. D., Gomes, H. M., Duppre, N., Sampaio, E. P., Alvin, I. M. P., Nery, J. A. C., Sarno, E. N. and Pessolani, M. C. V. Immunological cytokine correlates of protective immunity and pathogenesis in leprosy. Scand. J. Immunol. **51** (2000) 419–428.
6. Maury, C. P. J. Tumor necrosis factor—an overview. Acta Med. Scand. **220** (1986) 387–394.
7. Moubasher, A., Kamel, N. A., Zedan, H. and Raheem, D A. Cytokines in leprosy 1. Serum cytokine profile in leprosy. Int. J. Dermatol. **37** (1998) 733–740.
8. Silva, C. L. and Foss, N. T. Tumor necrosis factor in leprosy patients. J. Infect. Dis. **159** (1989) 787–790.
9. Tracey, K. J., Lowry, S. F. and Cerami, A. Cachectin: a hormone that triggers acute shock and chronic cachexia. J. Infect. Dis. **157** (1988) 413–420.